2011 Military Health System Conference

Military Infectious Diseases

Update on Vaccine Development

The Quadruple Aim: Working Together, Achieving Success

COL Julia Lynch, MD

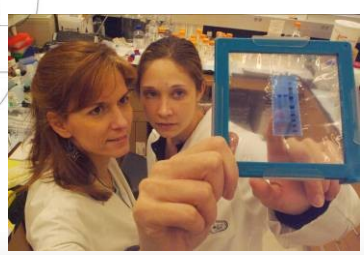
24 January, 2011

Medical Research and Materiel Command

Military Infectious Diseases Research Program (MIDRP)

To conduct for the Department of Defense, a
focused and responsive world class infectious
diseases research and development program
leading to **fielding of effective, improved means of protection and treatment**
to maintain maximal
global operational
capability with minimal
morbidity and mortality
- -Force Health Protection
- -Naturally Occurring Infectious Diseases


WRAIR/NMRC



Military Infectious Diseases Research Program (MIDRP)

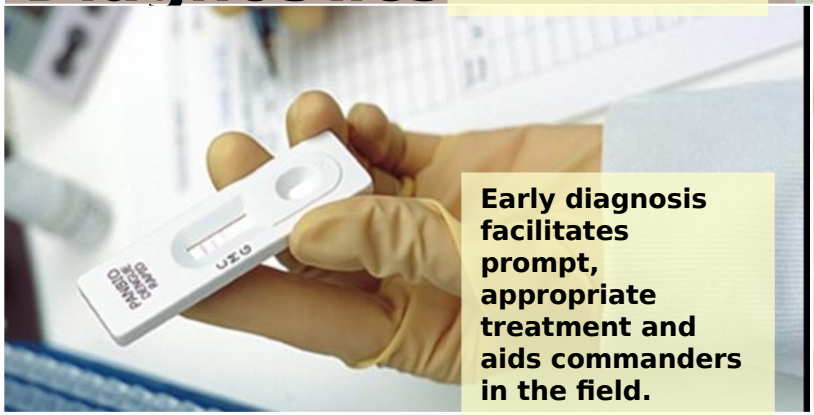
Prevention

Infectious diseases adversely impact military operations. Vaccines are the long-term solution.

Treatment

New drugs are continually required to overcome evolving drug resistance.

Diagnostics



Early diagnosis facilitates prompt, appropriate treatment and aids commanders in the field.

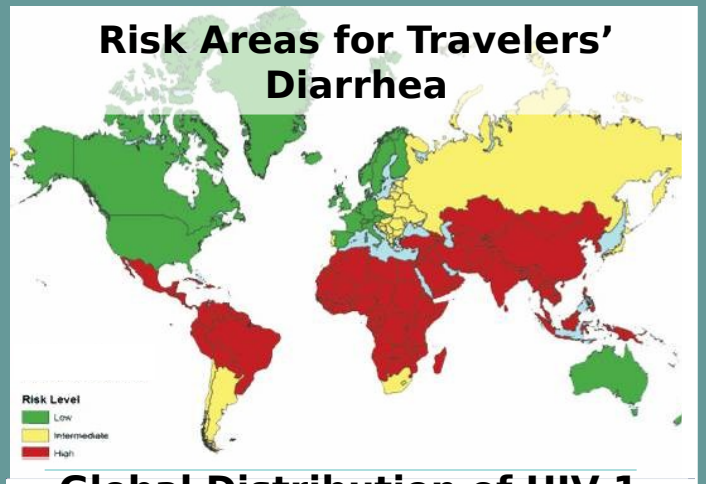
Insect Vector Control

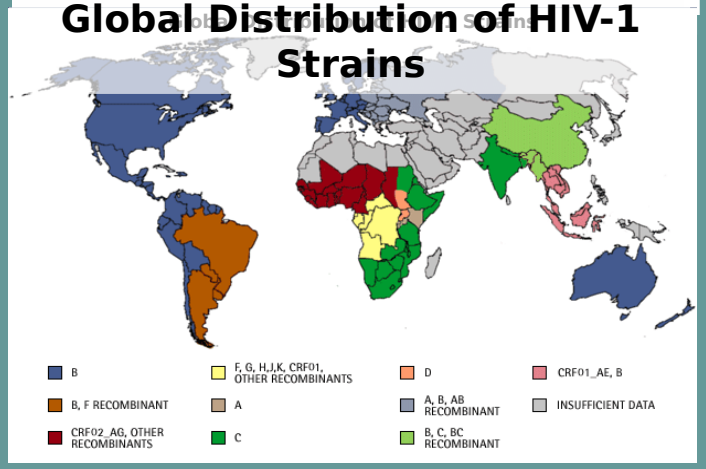
Most militarily relevant infectious diseases are transmitted by biting insects and other arthropods.

Naturally Occurring Infectious Diseases Impact U.S. Military Operations

Infectious Diseases…

- Can cause more casualties than enemy fire
- Are present wherever the military is deployed
- Require new tools to combat emerging diseases and evolving drug resistance



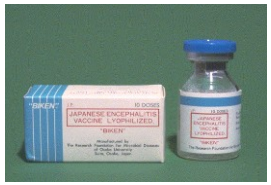


Military Cost…

- Lost duty time
- Decreased combat effectiveness
- Morbidity due to drug-related side effects
- Medical logistical burden

US Military Infectious Disease Products

	Research Effort	Advanced Development	Fielded Products
Antiparasitic Drugs	Malaria	Intravenous Artesunate Tafenoquine	Atovaquone/Proguanil (Malarone, 2000) Doxycycline (Vibramycin®, 1992) Halofantrine (Halfan®, 1992) Mefloquine (Lariam ®, 1989)
	Leishmaniasis	Pentostam Topical drug	Sulfadoxine-Pyrimethamine (1983) Chloroquine-Primaquine Tablets (1969)
Vaccines	Malaria Diarrhea Dengue Hemorrhagic fevers Scrub Typhus Meningitis	New Adenovirus Dengue Tetravalent HIV	Japanese Encephalitis - cell based (2009) Primaquine (1952) Chloroquine (1949) Hepatitis A (1995) Japanese Encephalitis (1992) Oral Live Typhoid Ty21A (1989) Hepatitis B (1981)
Protecta[illegible]	HIV Repellents Sand fly control Insect identification	Combined Camouflage Face Paint	Walter Reed Biosystematics Unit (2004) Meningococcus (A, C, Y, W-135) (1981) Adenovirus 4 & 7 (1980) West Nile Virus (2011)
Diagnosti	Laboratory-based assays Point of care devices	Leishmania PCR Leishmania Skin Test	Scrub Typhus Diagnostic Kit (1998) Malaria Rapid Diagnostic Test (2007) Malaria Diagnostic Kit (1996) DEET-based Insect Repellent (1946)



What Makes the MIDRP Unique?

- Focused on FDA/EPA approved products for the warfighter (adult indication)
  - Enhance global operational capability
  - Enhance Stability operations
- MRMC organized like a pharmaceutical company
  - Product development oriented organizational structure and processes
  - Decision Gate System integrates best industry business practices
  - Historical success of vaccines/therapeutics
- Core research program embedded in Military labs with uniformed researchers
  - Discipline and mission focus (requirements)
  - Global research platform – Host nation

"Because, if we fail to protect them, who will protect us?"
CAPT Meg Ryan

Critical Resource in Global Research

USAMRIID, Fort Detrick

WRAIR/NMRC, Silver Spring

NMRC-D, Lima

USAMRU-K, Nairobi

NAMRU-3, Cairo

AFRIMS, Bangkok

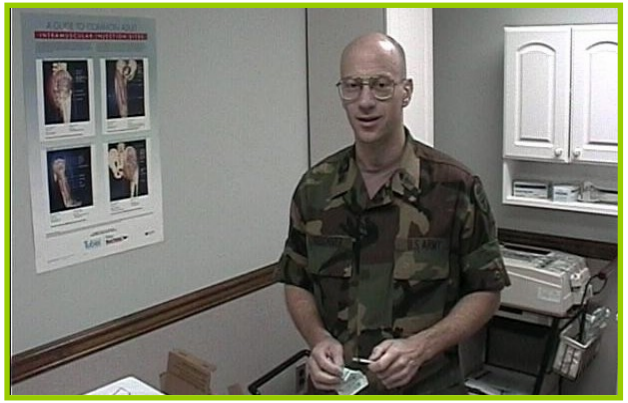
NAMRU-2, Jakarta

Other Assets

Accredited Lab Animal Facilities

Pilot Vaccine Production Facility

Biosafety Level 4 Containment



Clinical Trials Units

HIGH Research Quality

WEB OF SCIENCE Malaria Vaccine Research

26% of top 100 authors are Army and Navy Investigators

Authors Refine Exclude Cancel Sort these by: Record Count

The first 100 Authors (by record count) are shown. For advanced refine options, use Analyze results.

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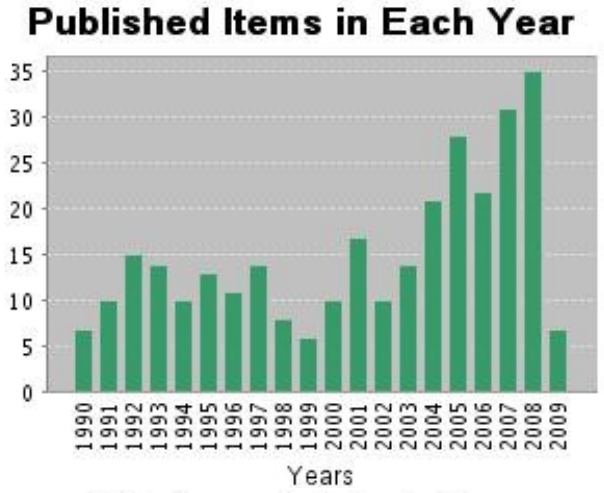
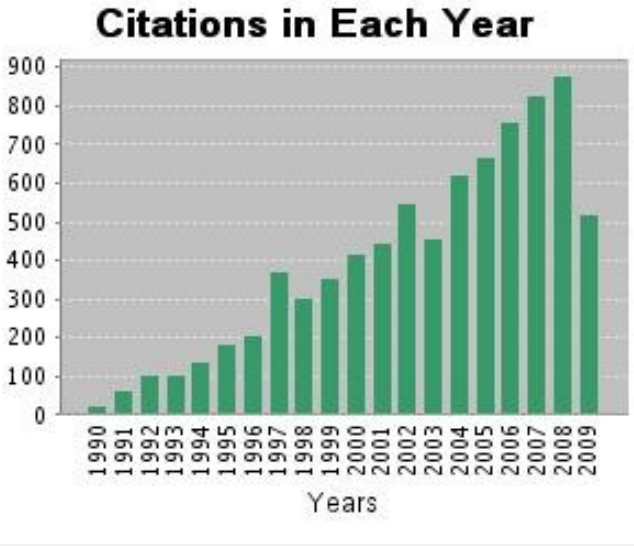


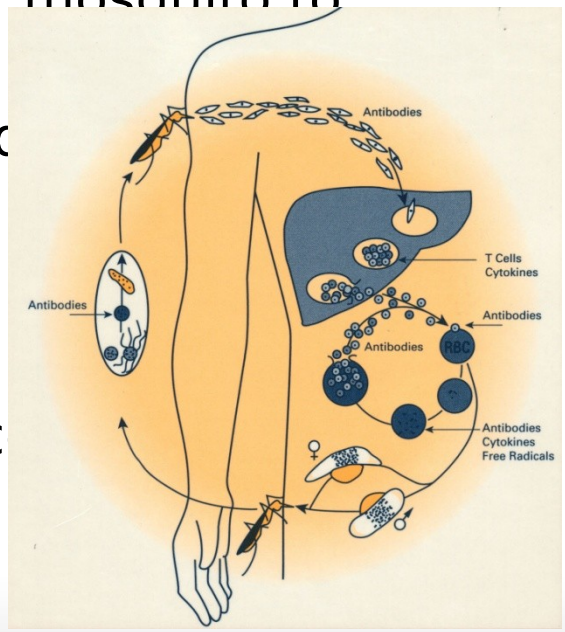


Vaccine Development Update

- Malaria
- Dengue
- Bacterial Diarrheal Pathogens
  - ETEC
  - Shigella
  - Campylobacter
- Top 3 Infectious Disease Threats
  - April 2010 ID Threat Prioritization Panel

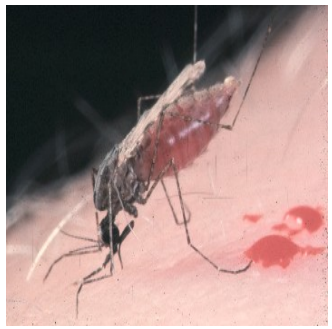
A little about Malaria

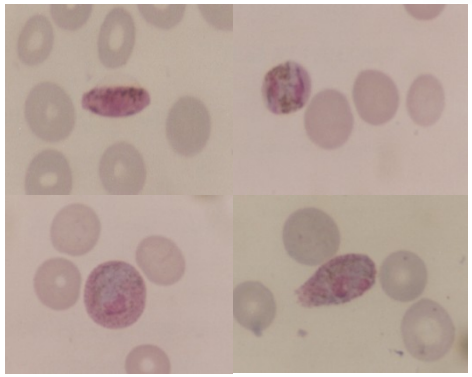
- Four Major Human Species: *Plasmodium falciparum , Plasmodium vivax, Plasmodium malariae and Plasmodium ovale.*
- Sporozoite stage injected in bite of female *Anopheles* mosquito, invades liver, matures/multiplies producing blood stages that invade host erythrocytes to cause disease, further matures and is ingested by another mosquito to complete life cycle.
- Acute febrile illness characterized by period
  fevers occurring every 48-72 hours
  - *Plasmodium falciparum- severe disease*
    cause coma and death
  - *Plasmodium vivax* -relapse or recrudesc
    over months or years
- Illness easily misdiagnosed

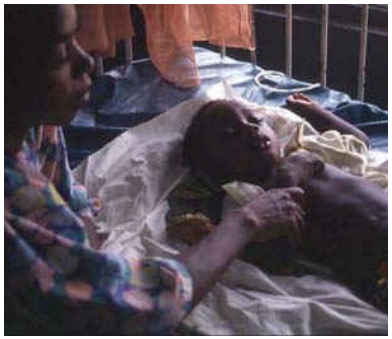


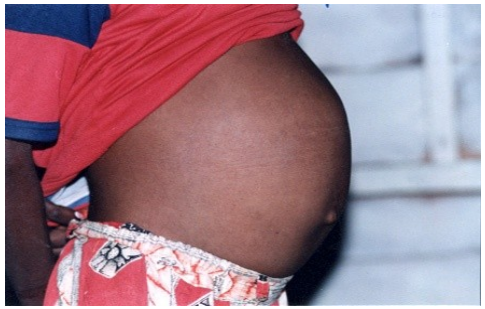
Burden of Malaria for Endemic Countries

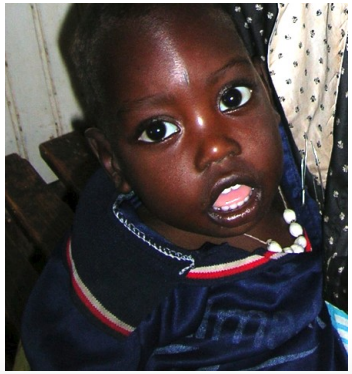
- 243 million cases
  - 85% Africa
  - 10% SE Asia
- 863,000 deaths
  - 89% Africa
  - 6% E. Mediterranean
  - 5% SE Asia
- Risk groups
  - Infants & young children
  - Pregnant women
  - Travelers



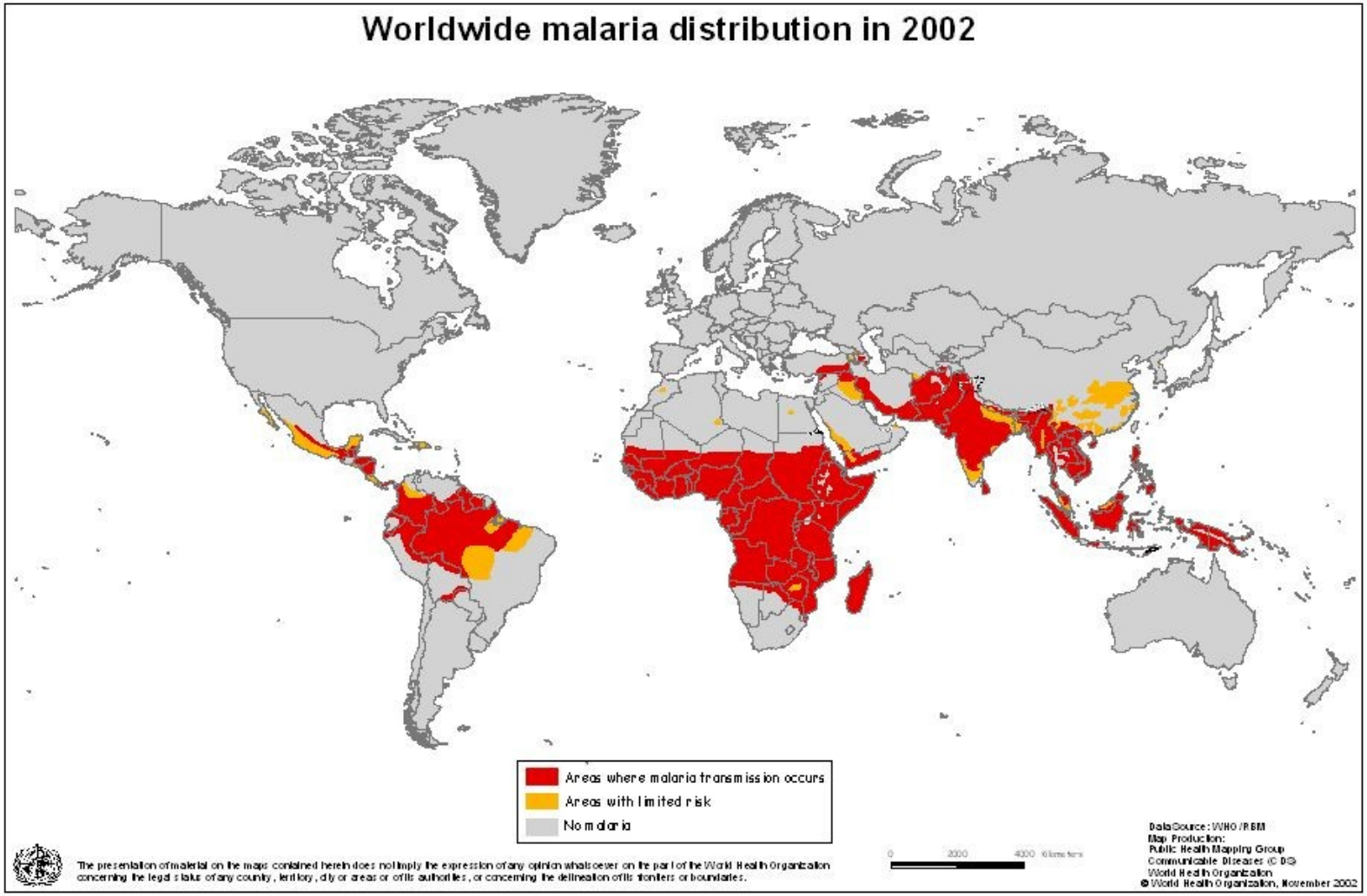




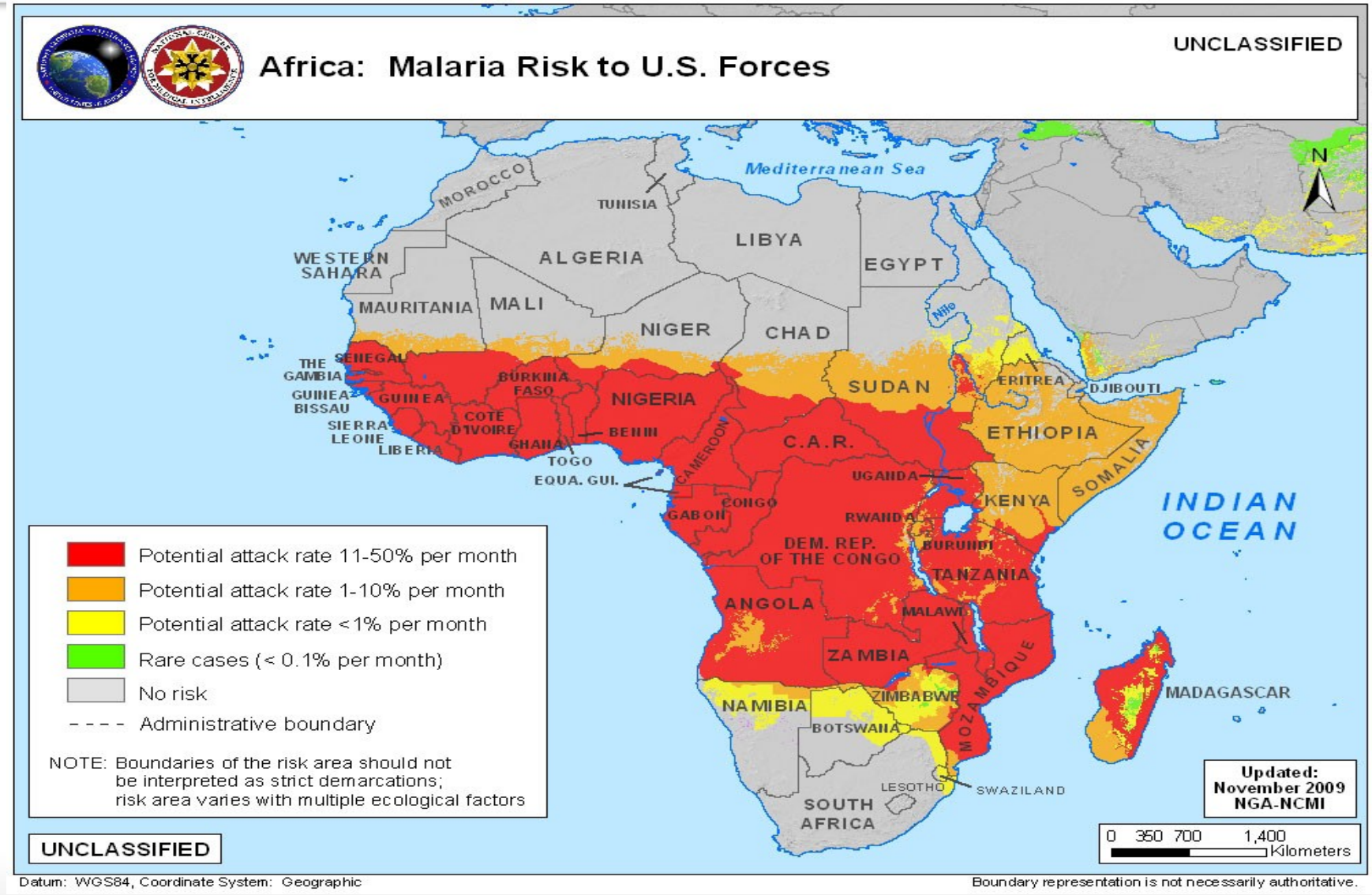




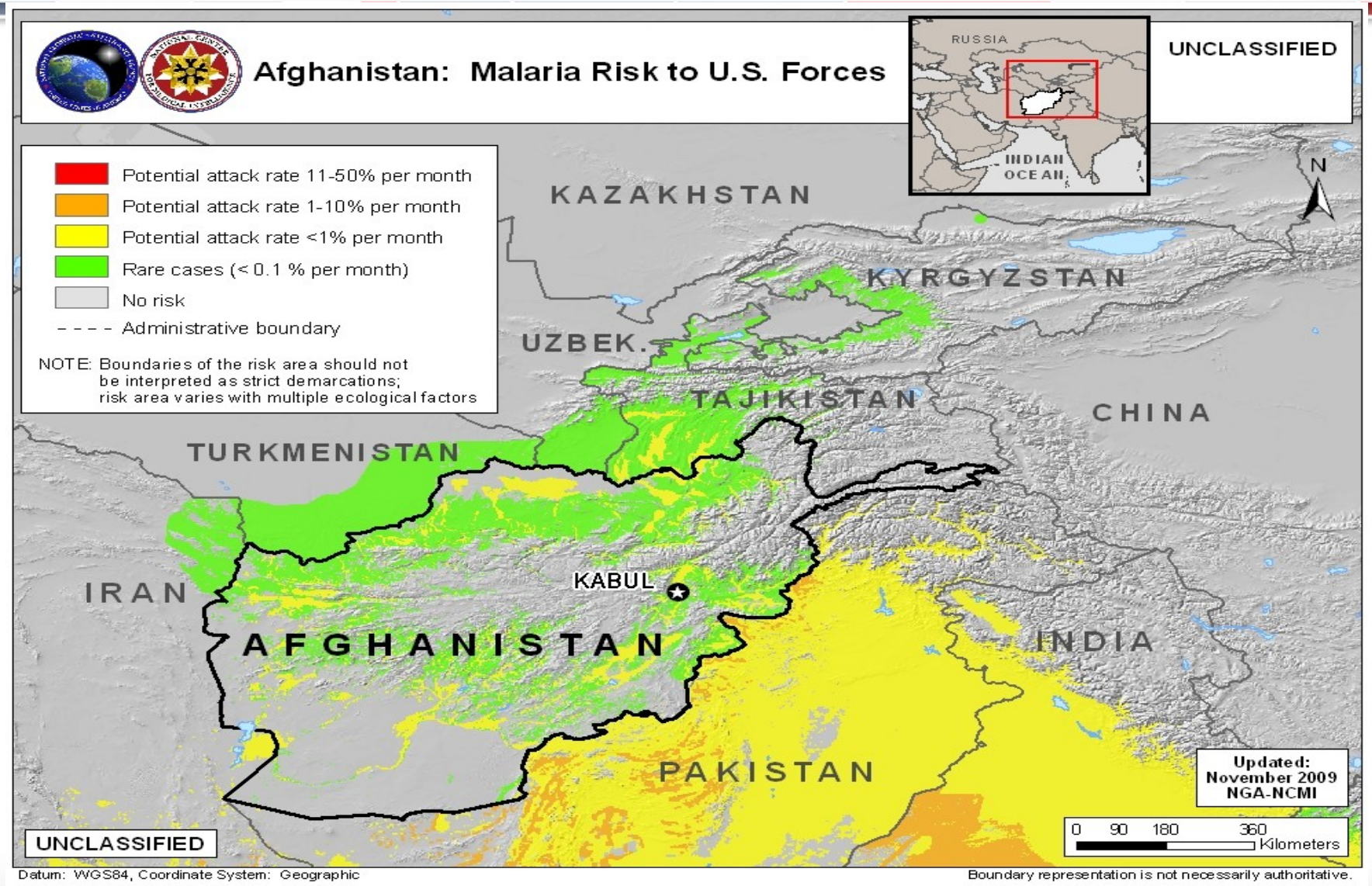
Worldwide Malaria Distribution



Malaria Risk Map



Malaria Risk Map



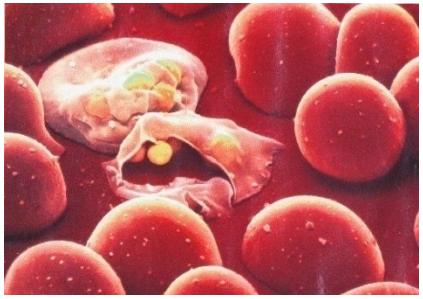
The Threat:

- Historically the most feared and disabling epidemic disease for deployed forces.
- 80-100% attack rates experienced by US forces in WWII in Guadalcanal and New Guinea.
- Relapsing *Plasmodium vivax* malaria emerged in US forces following Korean war.
- Chloroquine-resistant malaria afflicted US forces during Vietnam war.

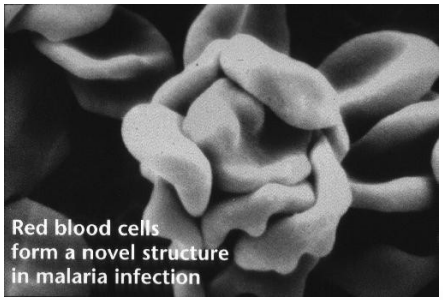
History of Recent Military Deployments

Country	Forces	Outcomes
Haiti-2010	US Army/Navy	13 Cases 6 Evacuations
Liberia-2003	US Marines ~225 for 2 Weeks	80 Cases 44 evacuation 4 Severe & Complicated
Afghanistan-2002	US Army Rangers 725 man force 4 months	38 cases
Nigeria-2001	US Special Forces 300 for Short Term Deployment	7 Cases 2 Severe and Complicated 1 Death

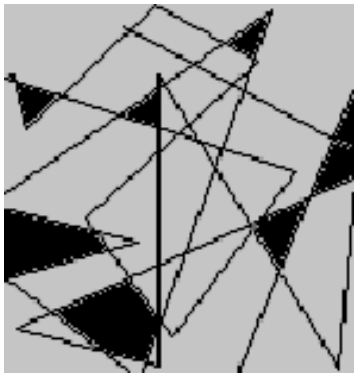
Naturally Acquired Immunity(model for preventing disease & death)



- No deaths or severe disease after 10 yr age
- > 95% of children < 5 y/o parasitemic
  - Deaths
    - Severe anemia (0-2 y/o)
    - Cerebral malaria (3-5 y/o)
- Decreased incidence, prevalence, and density of infection with age
- Mechanism: Antibodies ? Cellular?
- Antigenic targets: parasite proteins expressed on surface ?



Approaches to Malaria Vaccine Development



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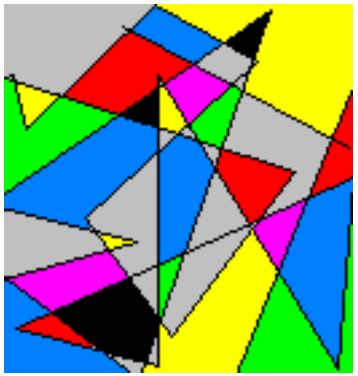


Individual antigens delivered <u>as subunit vaccine</u>

-Hep B SAg, Tet toxoid

- RTS,S/AS0 (protein-based)

- NMRC-M3V-D/Ad-PfCA (gene-based)

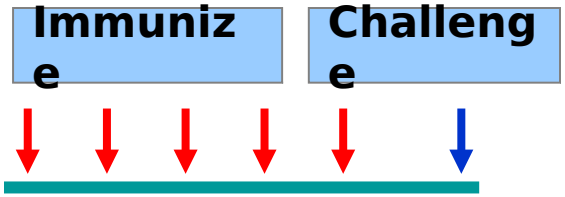
Many antigens delivered as <u>whole organism</u>

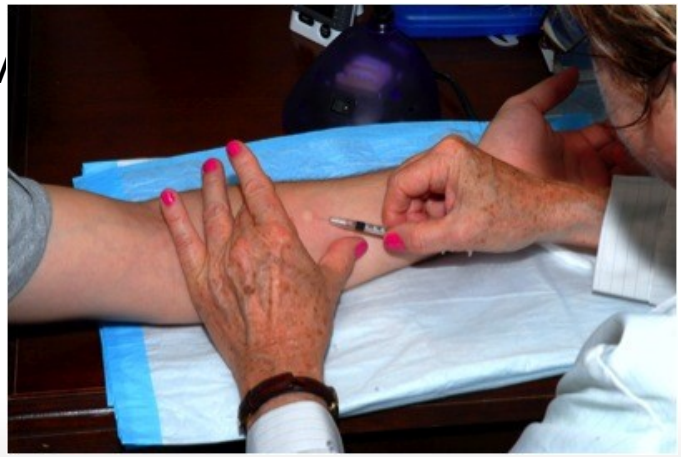
- Licensed live vaccines (polio, MMR)

- **Radiation-attenuated sporozoites**
- **Genetically-attenuated sporozoites**

Whole Organism Approach- Irradiated Sporozoite vaccine

- Irradiated sporozoite vaccine gives greater than 70% sterile protection when administered by mosquito bite in man.
  - Not strain specific, duration at least 9 months
- Process developed to harvest sporozoites from mosquito salivary glands to allow needle delivery
- 2010 Clinical Trial
  - Mosquito Derived Vaccine safe and well tolerated
  - Protection was substantially less than prior study (2/44)
  - Problem likely the dose, route of deliv and/or administration schedule

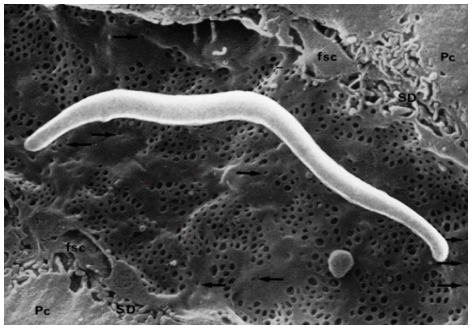




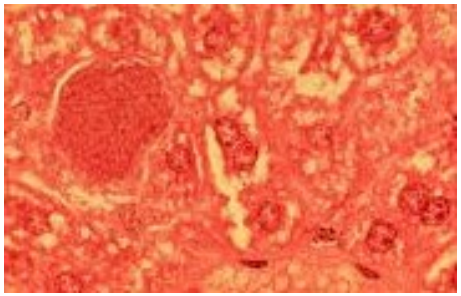
Sanaria, MVI/Gates Foundation, NIAID and USMMVP.

Whole Organism Approach- Attenuation of Sporozoite via Genetic Knock-out

- Parasite genetically engineered to lack two genes essential for maturation from liver stage to blood stage parasites.



- 2010 Clinical Trial at WRAIR
  - Delivery via infected mosquito bite
  - Breakthrough clinical infections



Seattle Biomedical , Gates Foundation, WEHI and USMMVP

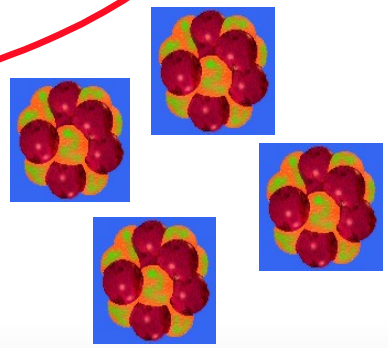
Subunit approach- RTS,S Vaccine

RTS,S is expressed
In yeast

PfCSP + Hepatitis B S Ag

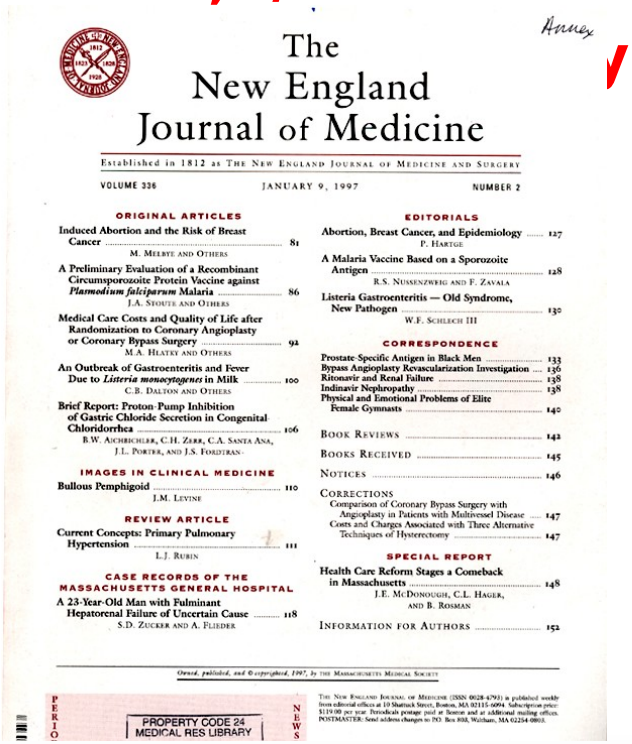
Repeats T epitopes S antigen

RTS,S particles assemble
during purification



Subunit approach- RTS,S Vaccine

6/7 subjects receiving RTS,S/AS02B



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A PRELIMINARY EVALUATION OF A RECOMBINANT CIRCUMSPOROZOITE PROTEIN VACCINE AGAINST *PLASMODIUM FALCIPARUM* MALARIA

José A. Stoute, M.D., Moncef Slaoui, Ph.D., D. Gray Heppner, M.D., Patricia Momin, Ph.D., Kent E. Kester, M.D., Pierre Desmons, Ph.D., Bruce T. Wellde, Ph.D., Nathalie Garçon, Ph.D., Urszula Krzych, Ph.D., Martine Marchand, W. Ripley Ballou, M.D., and Joe D. Cohen, Ph.D., for the RTS,S Malaria Vaccine Evaluation Group*

Abstract

Background The candidate vaccines against malaria are poorly immunogenic and thus have been ineffective in preventing infection. We developed a vaccine based on the circumsporozoite protein of *Plasmodium falciparum* that incorporates adjuvants selected to enhance the immune response.

Methods The antigen consists of a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) is expressed together with unfused HBsAg. We evaluated three formulations of this antigen in an unblinded trial in 46 subjects who had never been exposed to malaria.

Results Two of the vaccine formulations were highly immunogenic. Four subjects had adverse systemic reactions that may have resulted from the intensity of the immune response after the second dose, which led us to reduce the third dose. Twenty-two vaccinated subjects and six unimmunized controls underwent a challenge consisting of bites from mosquitoes infected with *P. falciparum*. Malaria developed in all six control subjects, seven of eight subjects who received vaccine 1, and five of seven subjects who received vaccine 2. In contrast, only one of seven subjects who received vaccine 3 became infected (relative risk of infection, 0.14; 95 percent confidence interval, 0.02 to 0.88; $P<0.005$).

Conclusions A recombinant vaccine based on fusion of the circumsporozoite protein and HBsAg plus a potent adjuvant can protect against experimental challenge with *P. falciparum* sporozoites. After additional studies of protective immunity and the vaccination schedule, field trials are indicated for this new vaccine against *P. falciparum* malaria. (N Engl J Med 1997;336:86-91.)

that inhibit the invasion of hepatocytes by sporozoites and induce cellular responses that kill sporozoite-infected liver cells.[2] Complete immunity against infection rarely develops from natural exposure, but immunization with radiation-attenuated sporozoites affords full protection.[3] This vaccine strategy is not practical, since it requires repeated exposure to hundreds of infected, irradiated mosquitoes over a period of 6 to 10 months, and sporozoites cannot be cultured in vitro. Nonetheless, these findings revealed a critical role for the circumsporozoite protein in the development of immunity against sporozoite challenge and led to its development as a candidate vaccine.[4,5] In clinical trials, however, the circumsporozoite protein is poorly immunogenic, and few subjects have been protected.[6] To address these issues, we created a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg. The resulting hybrid was significantly more potent than previous circumsporozoite-protein formulations.[7] We hypothesized that more potent adjuvants could improve the efficacy of the vaccine. We therefore conducted a clinical trial to determine the safety and efficacy of three formulations of circumsporozoite-protein vaccines against *P. falciparum*.

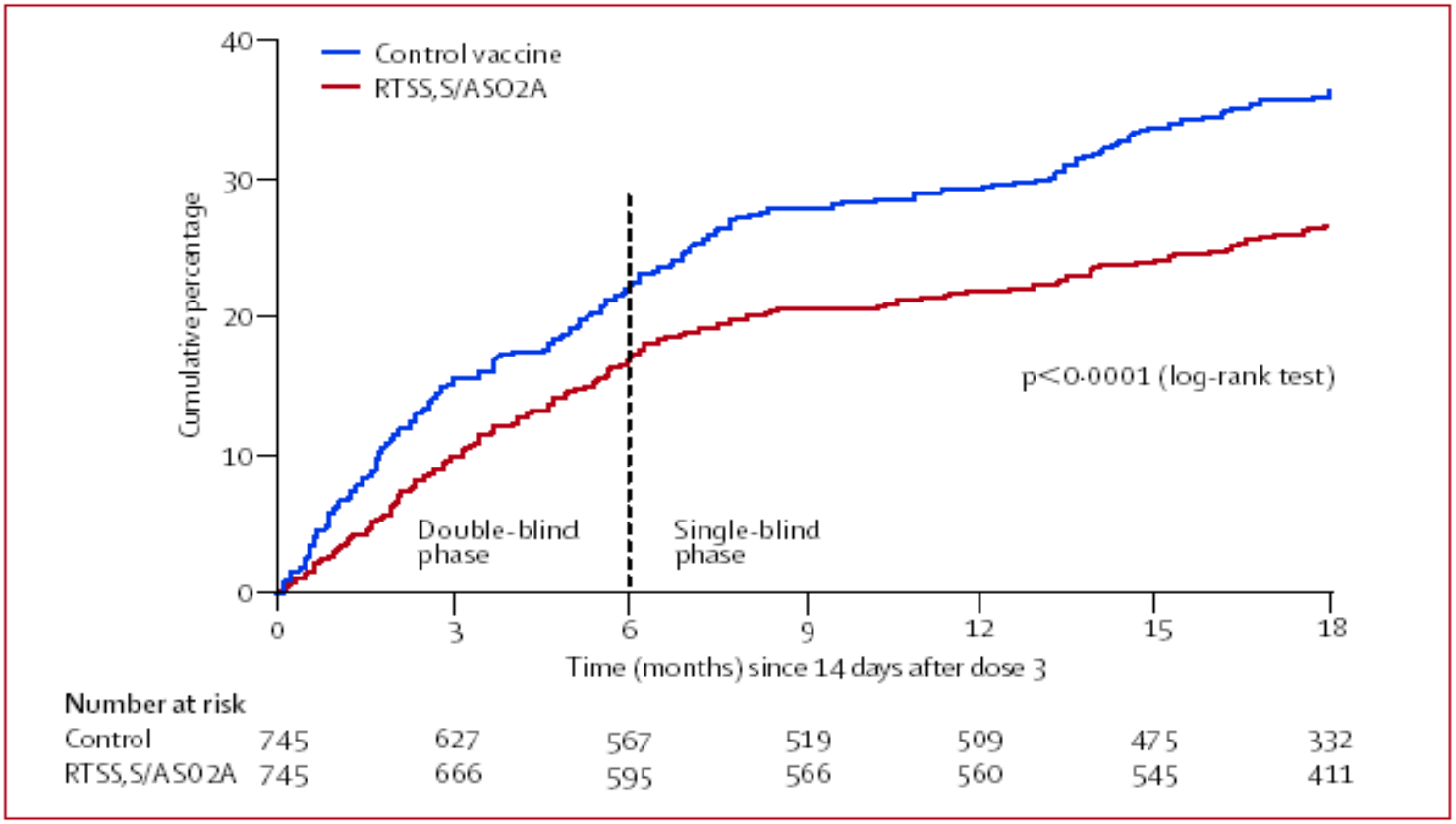
METHODS

Subjects

Forty-six subjects who had not been exposed to malaria (age, 18 to 45 years) were recruited by noncoercive means under a protocol approved by an institutional review board. Potential risks associated with participation in the study, including those associ-

Stoute JA et al. *N Engl J Med* 1997; 336(2):86-91

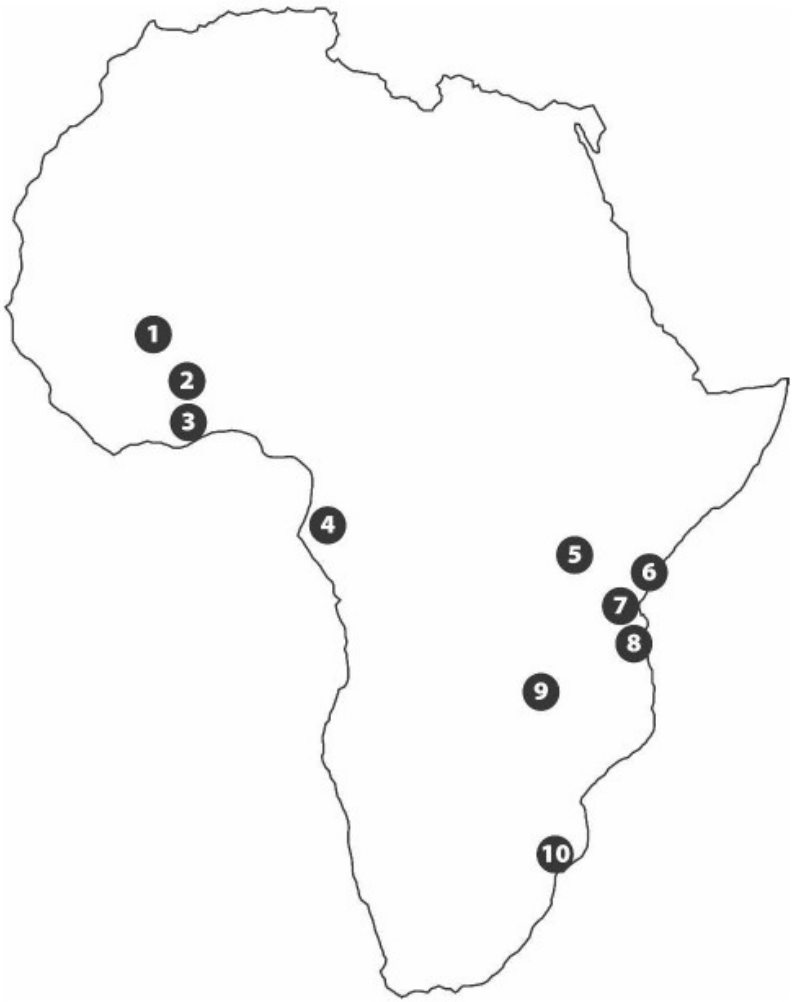
RTS,S Protects 1-4 yo Children in Mozambique



Alonso, Lancet 2005: Efficacy against clinical malaria 30% (CI: 8-45%)

Efficacy against severe malaria 49% (CI: 12-71%)

Subunit approach- RTS,S Vaccine



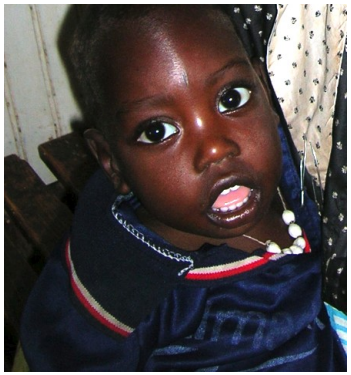
Sites across Africa where RTS,S is being tested in Phase 3

FIGURE 1. 1, Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso. 2, Kintampo Health Research Center (KHRC), Kintampo, Ghana. 3, Kumasi Center for Collaborative Research (KCCR)/School of Medical Sciences (SMS), Kumasi, Ghana. 4, Albert Schweitzer Hospital, Medical Research Unit Lambaréné, Gabon. 5, Kenya Medical Research Institute (KEMRI), Kisumu, Kenya. 6, KEMRI Wellcome Collaborative Research Program, Kilifi, Kenya. 7, Joint Malaria Program (JMP) Korogwe, Tanzania. 8, Ifakara Health Research and Development Center (IHRDC), Bagamoyo, Tanzania. 9, University of North Carolina Project, Lilongwe, Malawi. 10, Centro de Investigação em Saúde da Manhiça, Mozambique.

Ballou WR, Cahill CP. Am J Trop Med Hyg. 2007; 77(6 Suppl):289-95

Subunit approach- RTS,S Vaccine

- Licensure anticipated in ~2015 in Europe
  - Expected to be available in high endemic settings as a pediatric vaccine
  - Anticipate significant public health impact
  - Funded by MVI/Gates Foundation, EU, USAID and GSK with USMMVP support
- Efficacy insufficient for travelers' (thus military) vaccine
- Current studies in planning to improve efficacy through combination with other immunogen in a heterologous prime-boost approach



Subunit approach- DNA Prime/Ad Boost

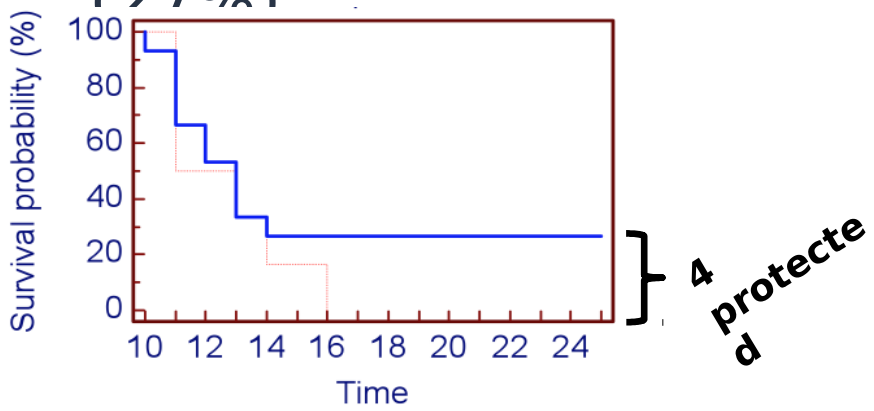
- DNA plasmids [Prime]
  - Encoding malaria proteins CSP and AMA1
- Adenovirus 5 (attenuated)[Boost]
  - Encoding malaria proteins CSP and AMA1

Uses host cell machinery to produce the malaria proteins

- Schedule of administration
  - 3x DNA
  - 1x Ad5
- Elicits strong cellular immunity (CD8>CD4)

Subunit approach- DNA Prime/Ad Boost

- **Clinical Results 2010- Proof of Principle**
  - 4/15 immunized volunteers sterilely protected (27%)

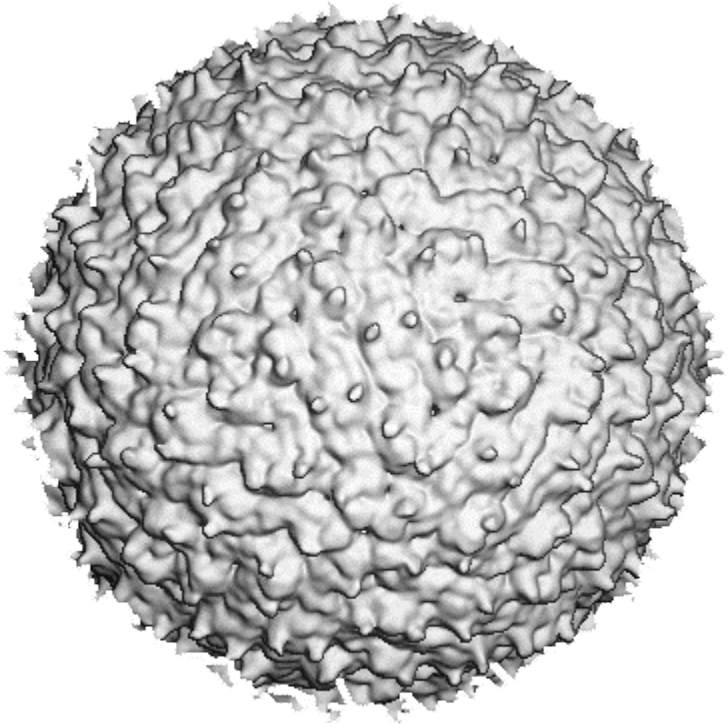


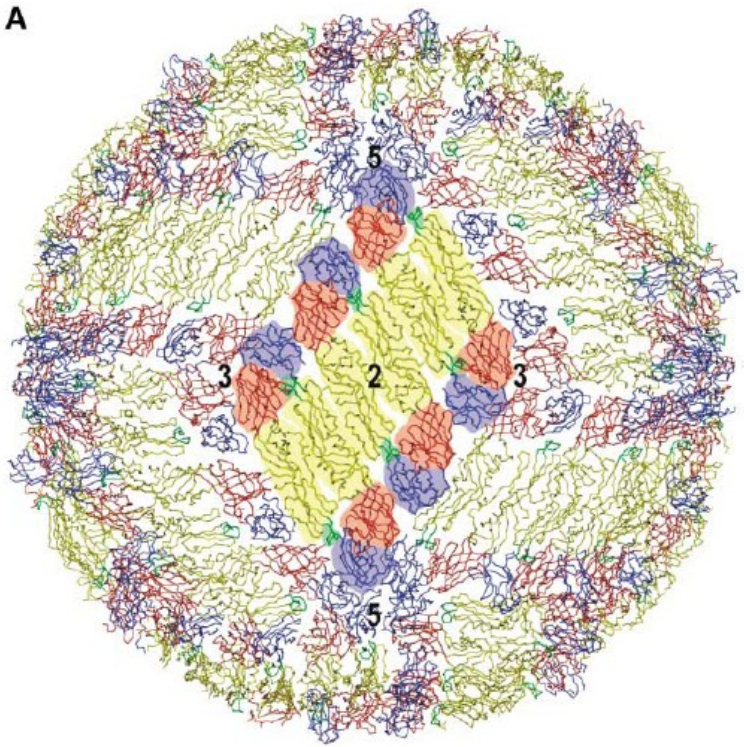
Day Post Challenge

- Major challenges to overcome to make this a viable product:
  - Improve protection
  - Require new Adenovirus-Malaria antigen construct
  - Regulatory requirements
  - Business complexity

USMMVP, USAID and GenVec

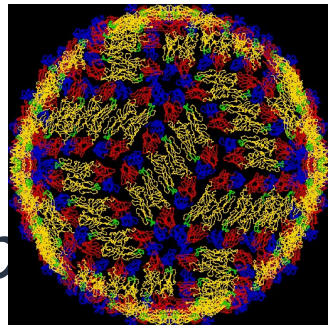
Dengue Vaccines

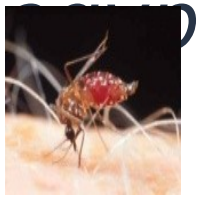




Dengue Background

- Dengue viruses
  - Single-stranded RNA viruses
  - *4 antigenically distinct serotyp*
    - *(DENV-1, -2, -3 and -4)*
- Transmission primarily by peridomestic mosquito species *Aedes a*
  - Daytime feeding
  - Domestic/Peridomestic habits
    - Breeds in freshwater containe
    - Thrives in urban environment

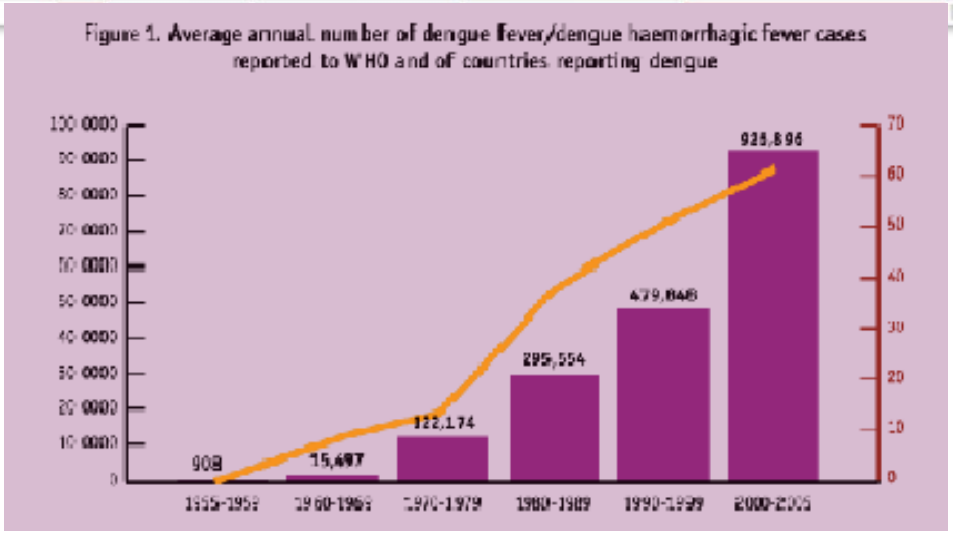




Dengue: Epidemiology

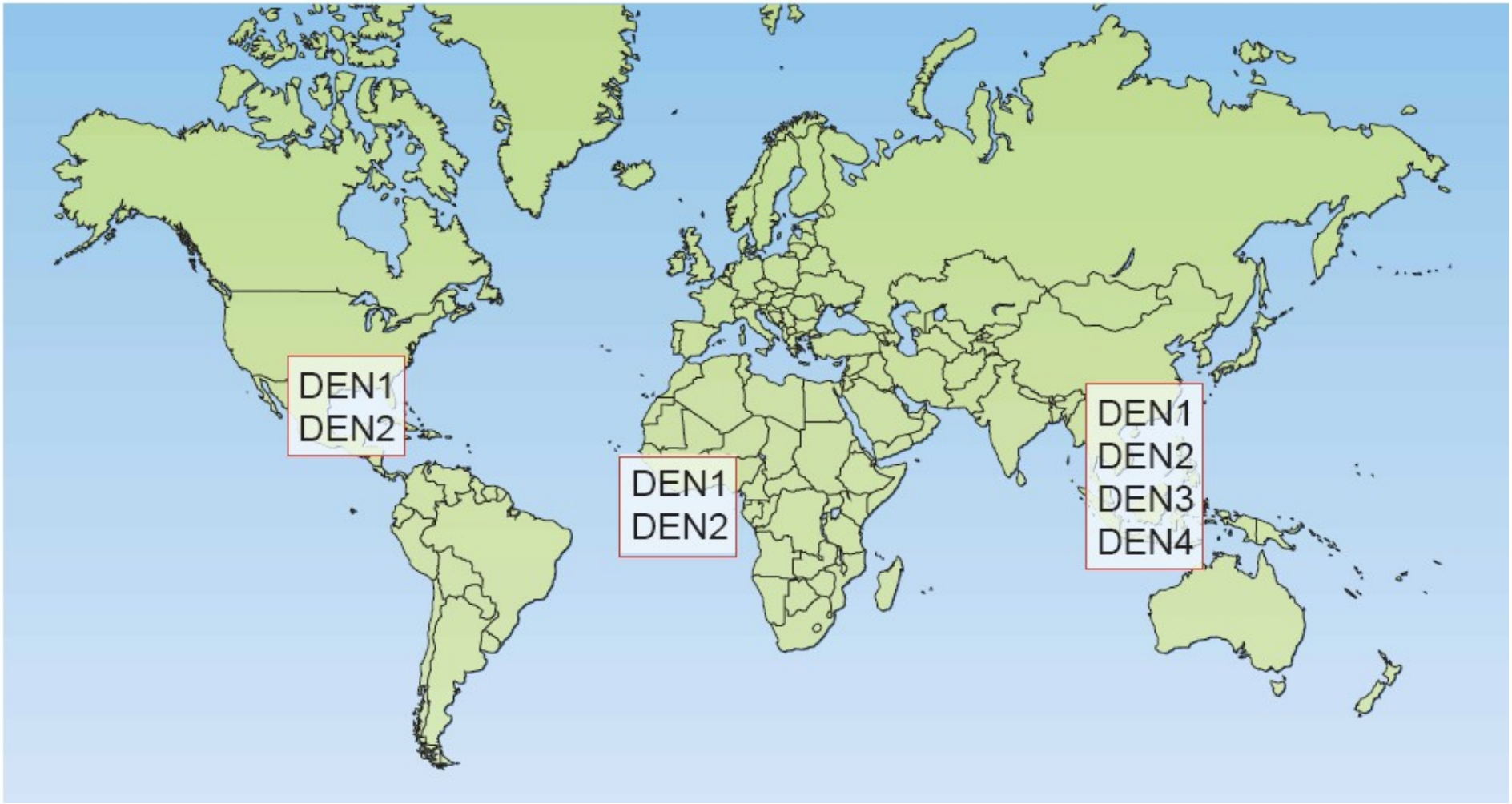
- Leading vector-borne viral disease globally
  - 2.5 billion people at risk for infection
  - Transmission in ~120 countries
    - Tropics and sub-tropics
    - *Humans are the reservoir*
  - 50 to 100 million infections annually
    - Undifferentiated Fever
    - Dengue Fever
    - Dengue Hemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS) ***secondary infections***
  - Up to 25,000 deaths annually

Global Resurgence of Dengue

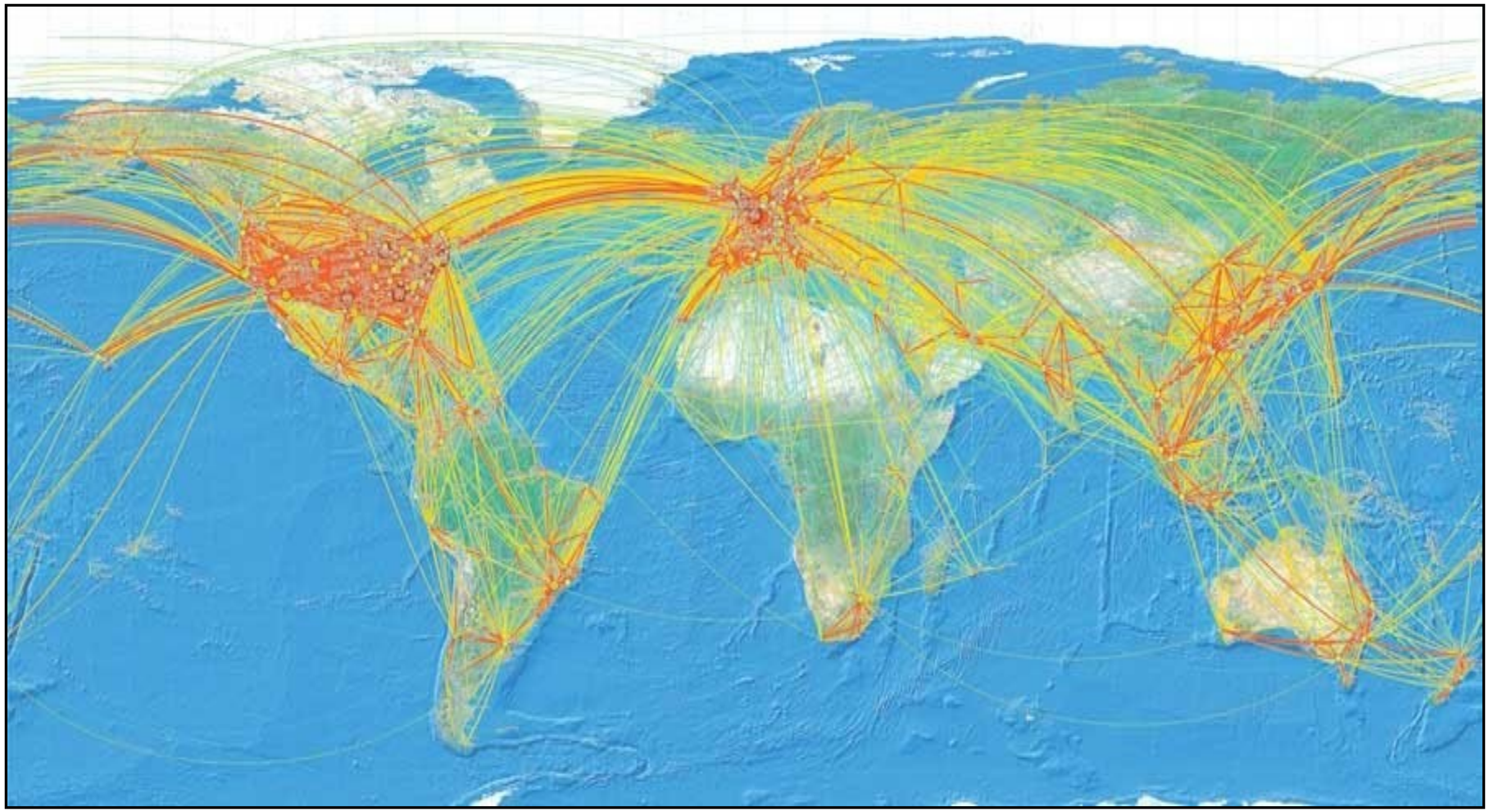


- Unprecedented global population growth
- Unplanned and uncontrolled urbanization
- Numerous man-made breeding grounds (trash)
- Lack of effective mosquito vector control
- Decay in public health infrastructure
- Increased international air travel

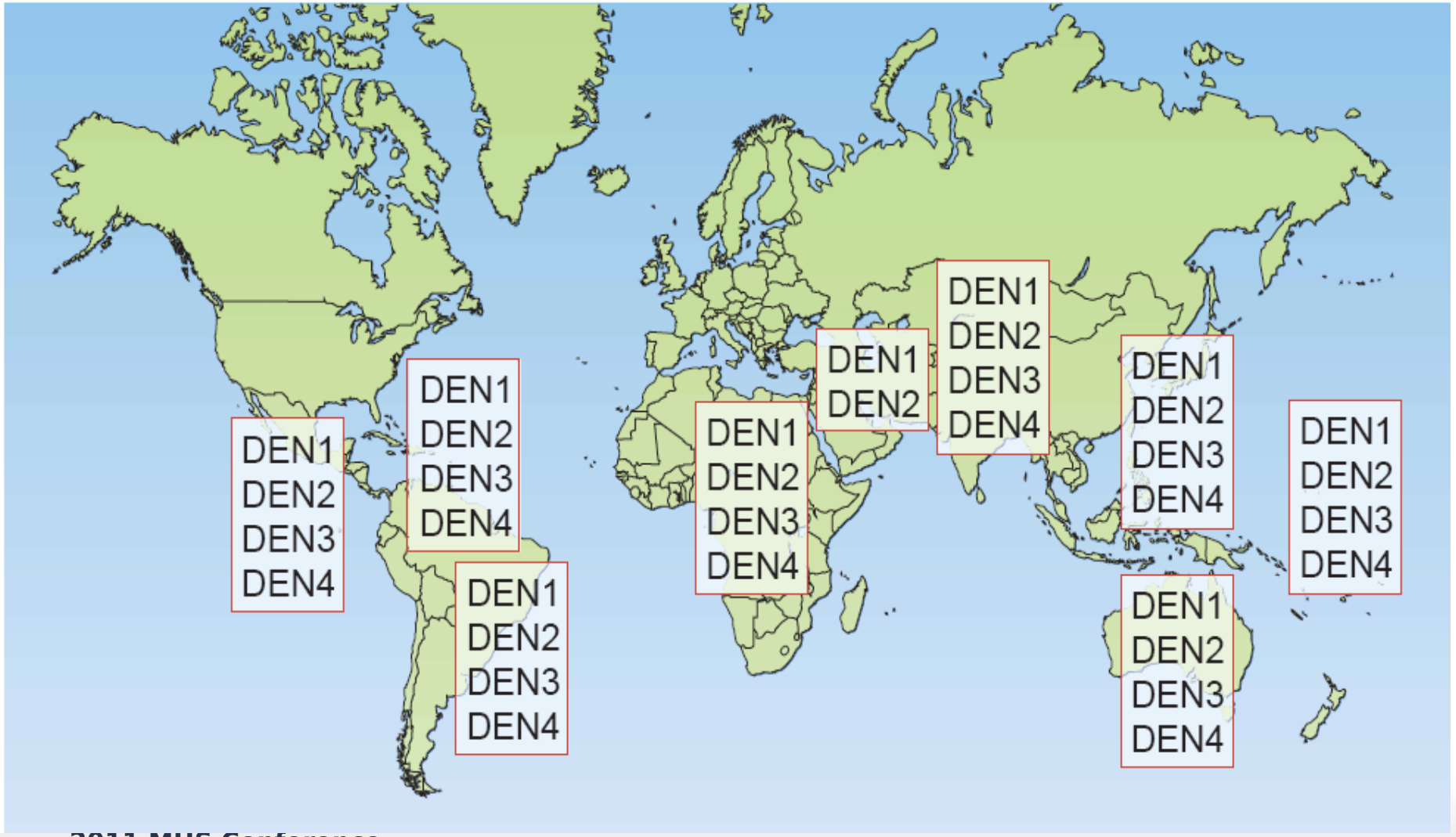
Global distribution of dengue virus serotypes, 1970



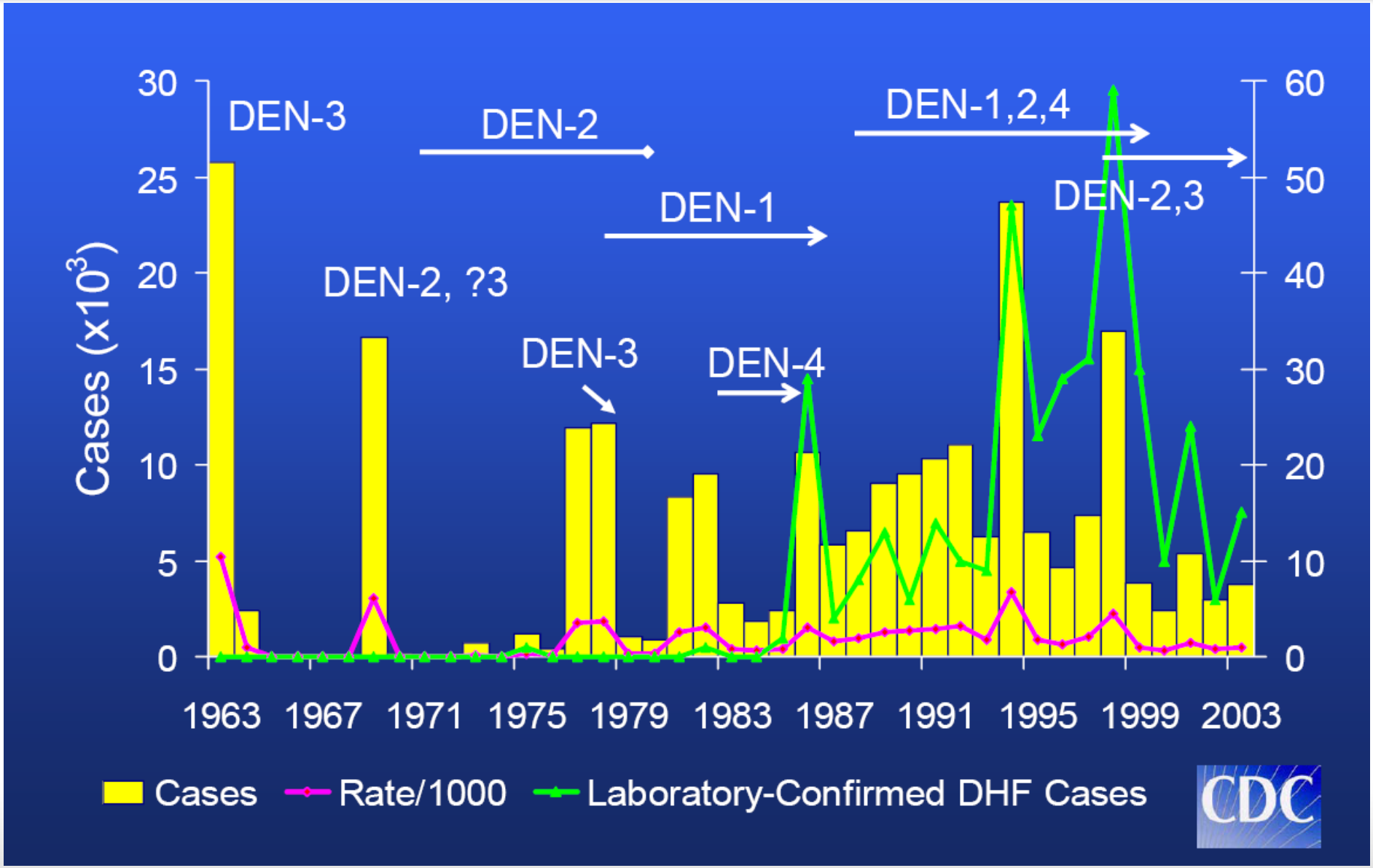
Air Traffic Global Flight Patterns



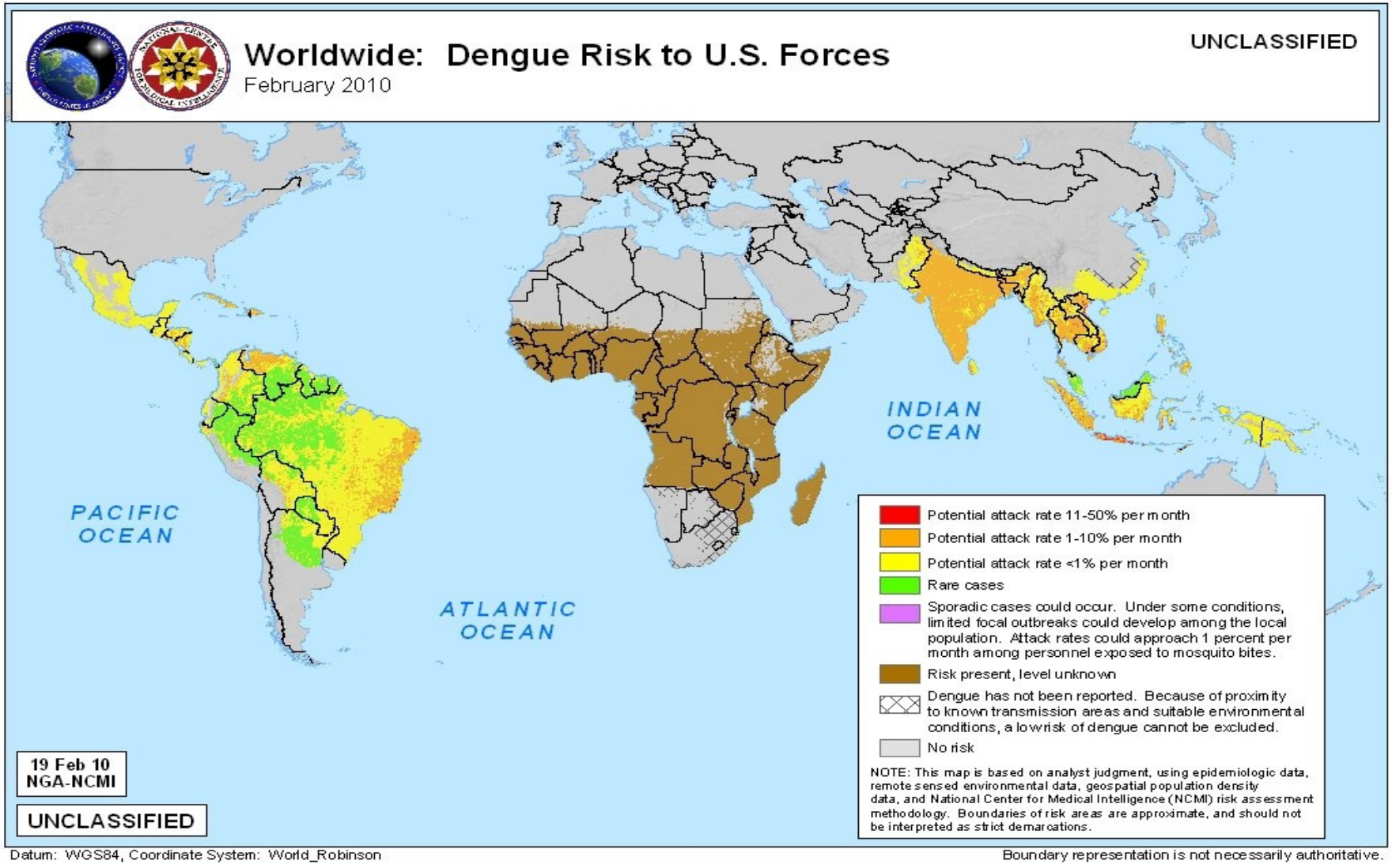
Global distribution of dengue virus serotypes, 2004



Dengue in Puerto Rico: 1963-2003



Dengue Risk


Worldwide: Dengue Risk to U.S. Forces
February 2010
UNCLASSIFIED
INDIAN OCEAN
PACIFIC OCEAN
ATLANTIC OCEAN
Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
Potential attack rate <1% per month
Rare cases
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.
Risk present, level unknown
Dengue has not been reported. Because of proximity to known transmission areas and suitable environmental conditions, a low risk of dengue cannot be excluded.
No risk
NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.
19 Feb 10
NGA-NCMI
UNCLASSIFIED
Datum: WGS84, Coordinate System: World_Robinson
Boundary representation is not necessarily authoritative.

Dengue Impact on the U.S. Military

- Philippines
- World War I
- Vietnam
- Philippines
- Haiti
- Somalia

Fort McKinley, Philippines

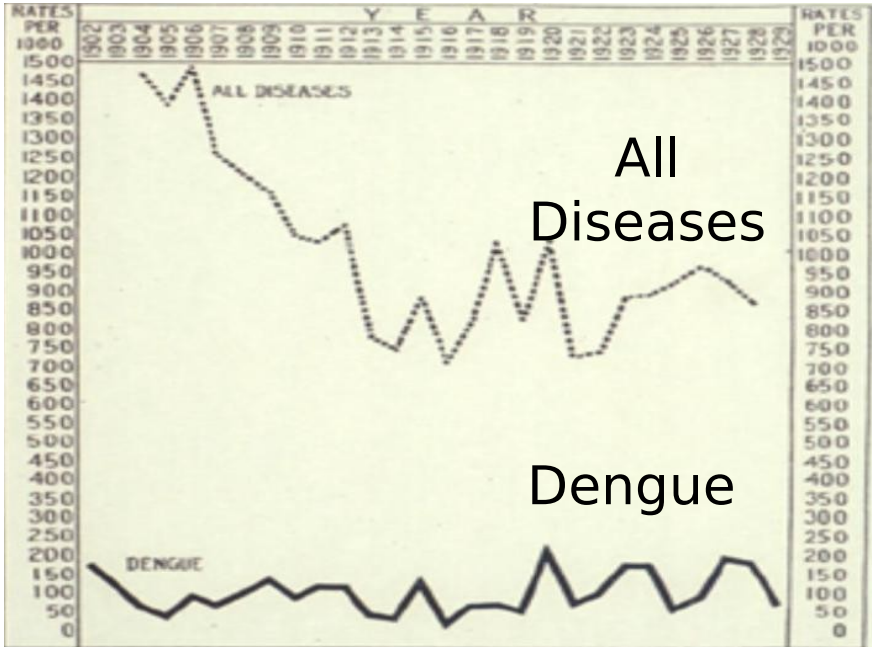
Dengue Outbreak: July – November 1906

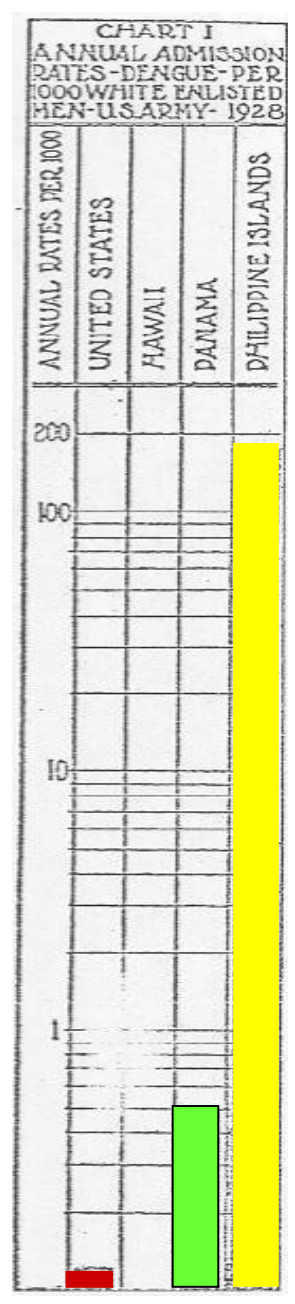
~1/3 of troops infected

Unit	Strength	No. Cases	% Infected
13th U.S. Infantry	727	240	33
16th U.S. Infantry	613	162	26
8th U.S. Cavalry	378	89	24
Total	**1718**	**491**	**29**

Philippine Islands: 1902-1928

- Hospital admission rates
  - Decreases for all diseases
  - Consistent for dengue
- Average loss to Army of 7,715 days per year





Daily Reported Cases During the Saipan Dengue Epidemic, Sep - Oct 1944

-Dengue appears after 15 June island assault
-By 11 Aug, *Aedes* species numerous (rainy season)
-Combat operations created numerous breeding habitats (trash, tire ruts in roads…)

TABLE 12.—*Daily report of new cases*[1] *of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944*

Date	Number	Date	Number
1944		*1944*—Continued	
September 14	393	September 26	62
15	426	27	87
16	294	28	79
17	306	29	71
18	289	30	44
19	275	October 1	36
20	230	2	33
21	137	3	27
22	137	4	28
23	112	5	32
24	93	6	23
25	81		

[1] Cases include Army, Navy, and Marine Corps personnel.

Recent Experience

- 1966 - Long Binh, Vietnam
  - 110 Cases of FUO at 93rd Evacuation Hospital
  - **28% were determined to be dengue by viral isolation or serology**
- 1992 - Operation Restore Hope, Somalia
  - 129 hospitalized with FUO
  - **60% were determined to be dengue by viral isolation or serology**
- 1997 - Haiti
  - 103 hospitalized with FUO
  - **29% were determined to be dengue by viral isolation or serology**

Dengue

- Currently no U.S. FDA approved vaccine or pharmaceutical to protect or treat the Warfighter
- Current standard of care:
  - Supportive care
    - Careful fluid management and other supportive measures (10-14 LDD per episode)
  - Prevention
    - Effective vector control proven very difficult (requires sustained usage of products)
    - Personal Protective Measures (PPM) (repellents, bed nets, treated uniforms) difficult to sustain

Dengue and the US Military

- Mission-stopping disease threat to U.S. forces deployed throughout the tropics/sub-tropics
- #2 on US Military Infectious Disease Threat list

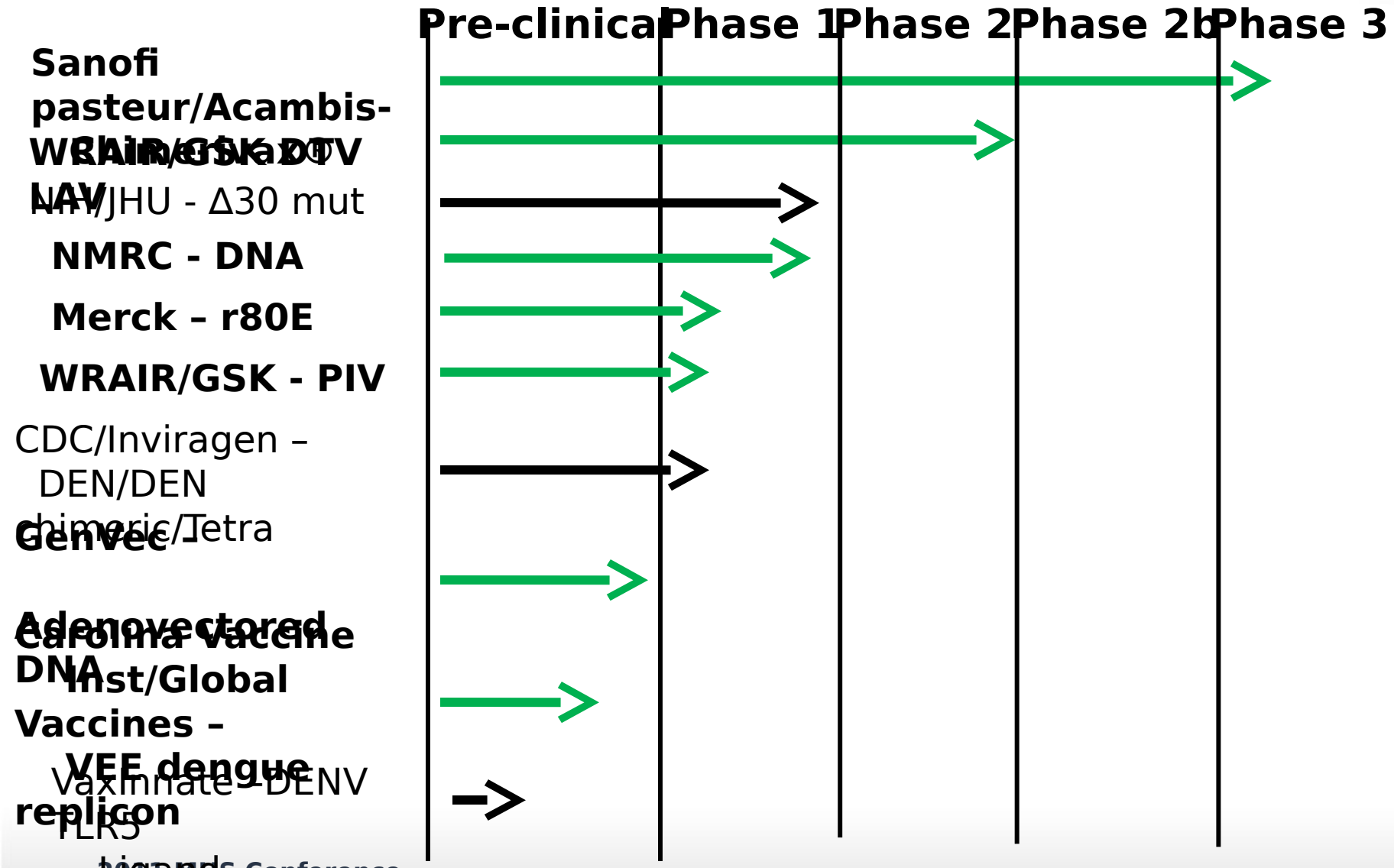
Target Product Profile

- Safety
  - Well tolerated injection
  - Does not cause dengue
  - Does not > risk of disease severe disease with secondary infection
- Efficacy
  - Vaccine Efficacy ≥ 80%
  - Durable immune response (>2 years)
  - 1-3 doses

Challenges in Dengue Vaccine Development

- Multiple (4) serotypes (4 vaccines in one)
  - Each capable of producing DF and DHF
  - Disease enhancement: Risk of DHF enhanced by pre-existing immune response to another serotype
- Lack of an animal model of disease
- Unknown Surrogate marker of protection
- Incomplete understanding of pathophysiology

Dengue Vaccine Landscape



Tetravalent Dengue Virus (TDV) Vaccine – Landscape

- Chimerivax®
  - Chimeric of yellow fever vaccine backbone with Dengue membrane proteins
  - Safe, well tolerated and immunogenic in clinical studies
  - Dosing schedule: 0, 6, 12-month
  - Starting Phase 3 clinical trials FY11
    - AFRIMS
      - » Thailand, Philippines
  - Uncertain whether dosing schedule or level of efficacy will meet DoD needs

Virology Field Site Kamphaeng Phet Province

Pivotal Trials Conducted by MRMC/Thai MoPH

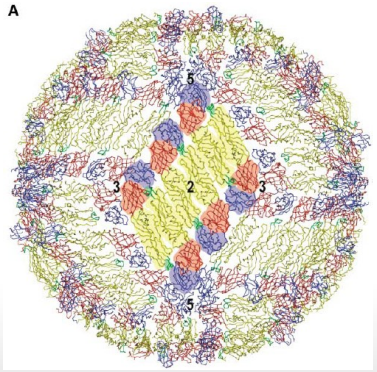
Japanese encephalitis Virus (JE-VAX®) 1980's
- -Biken

Hepatitis A Vaccine (Havrix) 1990's
- -GSK

Dengue vaccine (Chimerivax) (2011)

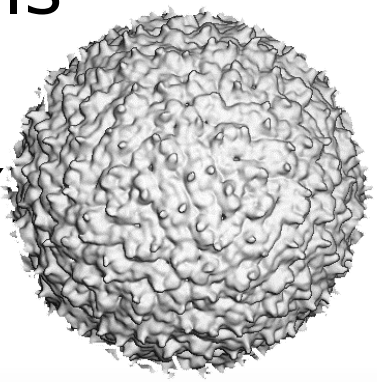
Tetravalent Dengue Virus (TDV) Vaccine - Landscape

- Live attenuated vaccine (LAV)
  - Viruses (classically) attenuated through serial passage in non-human cell line
  - Tetravalent formulation required balancing
  - 2 doses : 0, 6 months
  - 100% protection in animal models
  - Safe and immunogenic in human trials
    - Phase 2 study Puerto Rico
      - » 700 subjects
      - » 2-50y
      - » Safe and immunogenic
    - Phase 3



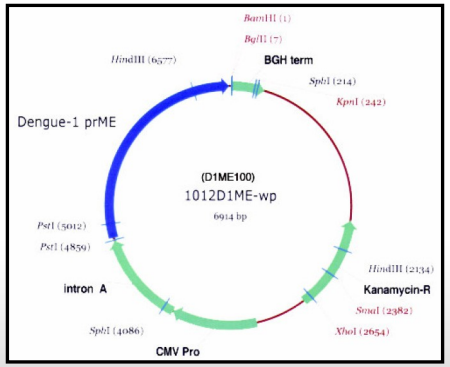
Tetravalent Dengue Virus (TDV) Vaccine - Landscape

- Purified inactivated virus (PIV)
  - Formalin inactivated, purified virus
  - Combined with adjuvants
    - Alum adjuvant
    - Novel adjuvants (GSK)
  - 100% protection in animal models
  - Shorter administration schedule
  - Phase 1 clinical trials begin in FY



Tetravalent Dengue Virus (TDV) Vaccine - Landscape

- DNA Vaccine
  - DENV DNA vaccine – closed circula double-stranded plasmid DNA
  - Full length genes encoding membrane proteins for DENV
  - Initial Phase 1 clinical study with DENV-1 DNA vaccine safe and immunogenic
  - TDV DNA Phase 1 clinical trial planned in 2011/12



Tetravalent Dengue Virus (TDV) Vaccine – Landscape

- Heterologous Prime Boost Strategy
  - Assess sequentially delivered combinations of different immunogens
    - Increase and broaden immune response
    - Shorten time to development of protective response
  - Live attenuated (replicating) immunogen combined with non-replicating
    - PIV
    - DNA
  - More complex business development
  - More complex logistics
  - Suitable for DoD

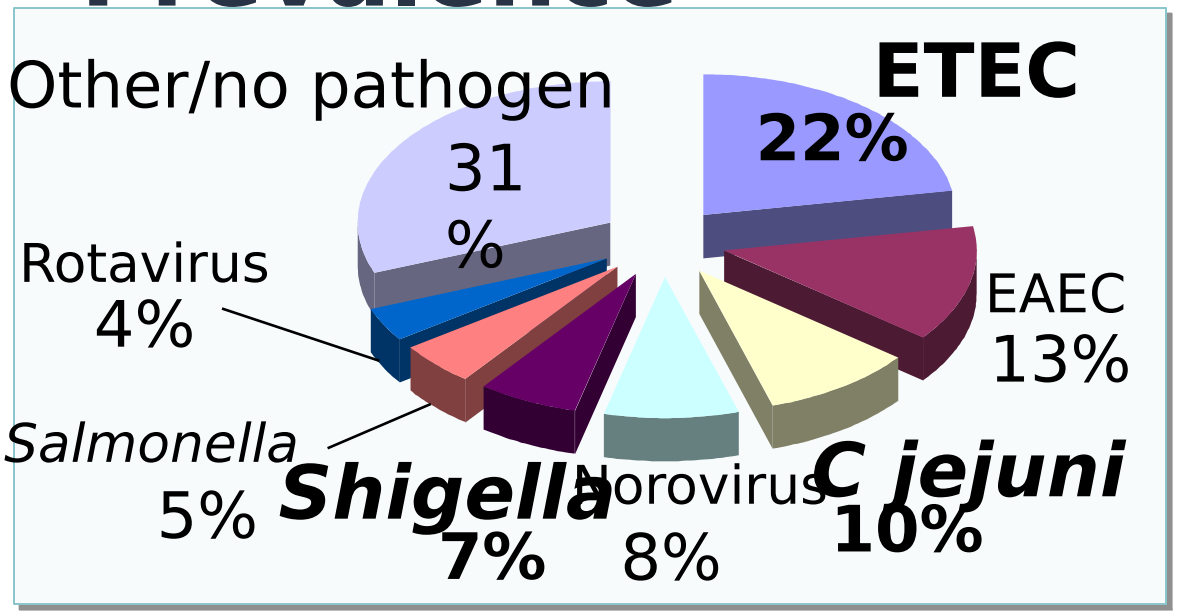
Vaccines Against Bacterial Diarrhea and Dysentery

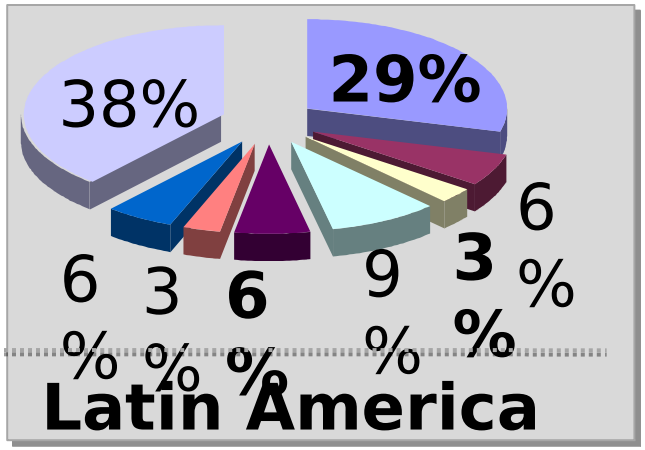
- Prevention of Diarrheal Diseases
  - Develop effective vaccines and other counter-measures against leading causes of infectious diarrhea and dysentery in deployed U.S. military personnel
  - Major research and development thrusts
    - Enterotoxigenic *Escherichia coli* (ETEC) vaccines
    - *Shigella* vaccines
    - *Campylobacter jejuni* vaccines

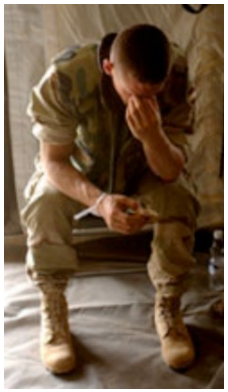
Vaccines Against Bacterial Diarrhea and Dysentery - Burden

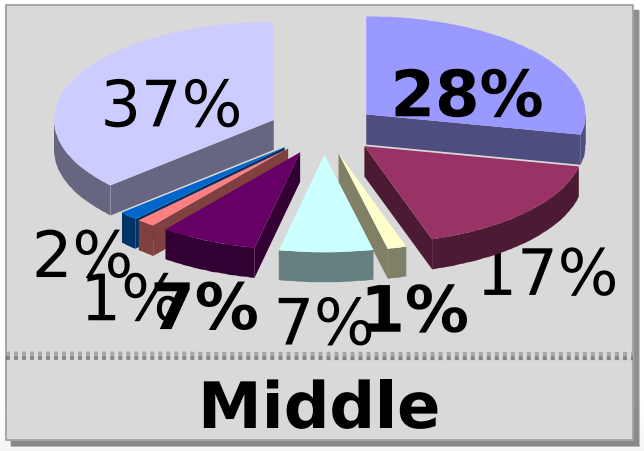
- **Cumulative deployments and diarrhea/dysentery burden OEF/OIF ’01-’07**
  - # of deployments (mean 183 d) 2,134,578
  - # of deployments (mean 19 d) 145,871
  - Cases of diarrhea 3,857,002
  - Diarrhea days 11,478,270
  - Visits to medical 850,444
  - Hospitalizations 17,356

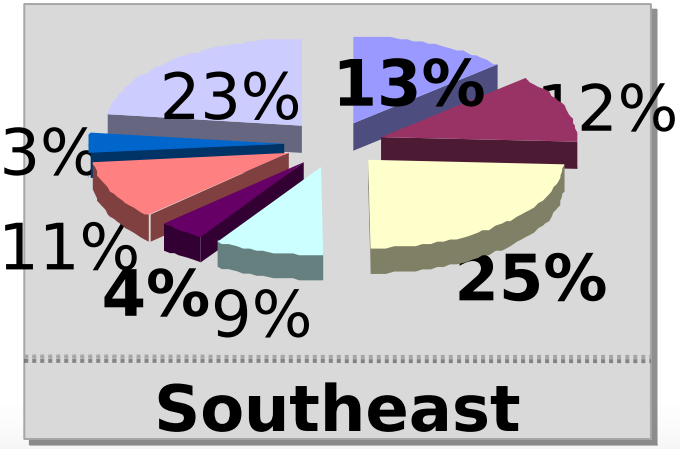
Vaccines Against Bacterial Diarrhea and Dysentery - Prevalence





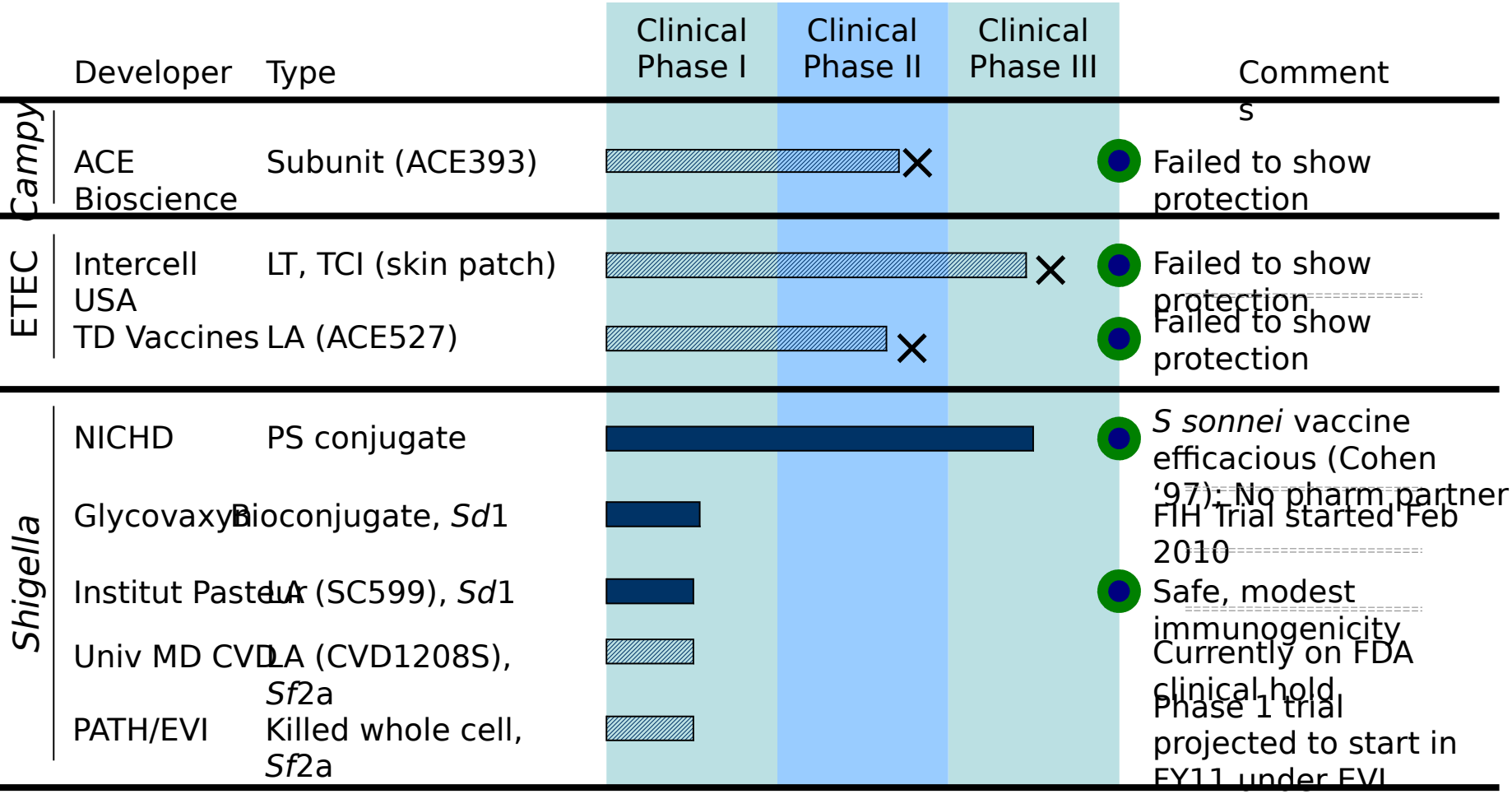






MS Riddle et al. *Am. J. Trop. Med. Hyg.*, 74(5), 2006

Vaccines Against Bacterial Diarrhea and Dysentery

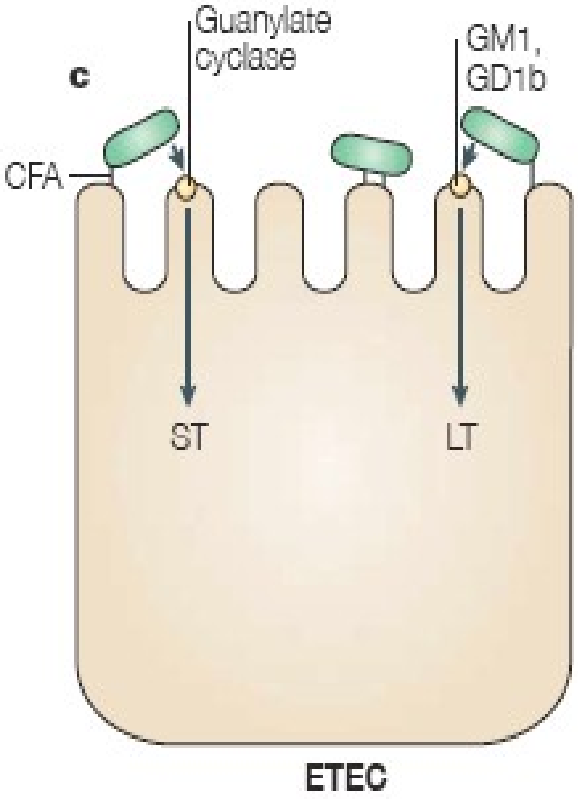


	Developer	Type	Comments
Campy	ACE Bioscience	Subunit (ACE393)	Failed to show protection
ETEC	Intercell USA	LT, TCI (skin patch)	Failed to show protection
	TD Vaccines	LA (ACE527)	Failed to show protection
Shigella	NICHD	PS conjugate	*S sonnei* vaccine efficacious (Cohen '97); No pharm partner
	GlycoVaxyn	Bioconjugate, *Sd*1	FIH Trial started Feb 2010
	Institut Pasteur	LA (SC599), *Sd*1	Safe, modest immunogenicity
	Univ MD CVD	LA (CVD1208S), *Sf*2a	Currently on FDA clinical hold
	PATH/EVI	Killed whole cell, *Sf*2a	Phase 1 trial projected to start in FY11 under EVI

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- At risk populations
  - Military / Civilian travelers
    - Leading cause of travelers' diarrhea
  - Endemically exposed individuals
    - 500K deaths annually in young children
  - Major disease in young farm animals (calves, piglets)
    - Characterized by different colonization factors

Pathogenesis



*from JB Kaper et al *Nature Rev Microbiol* 2004;2:123.

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

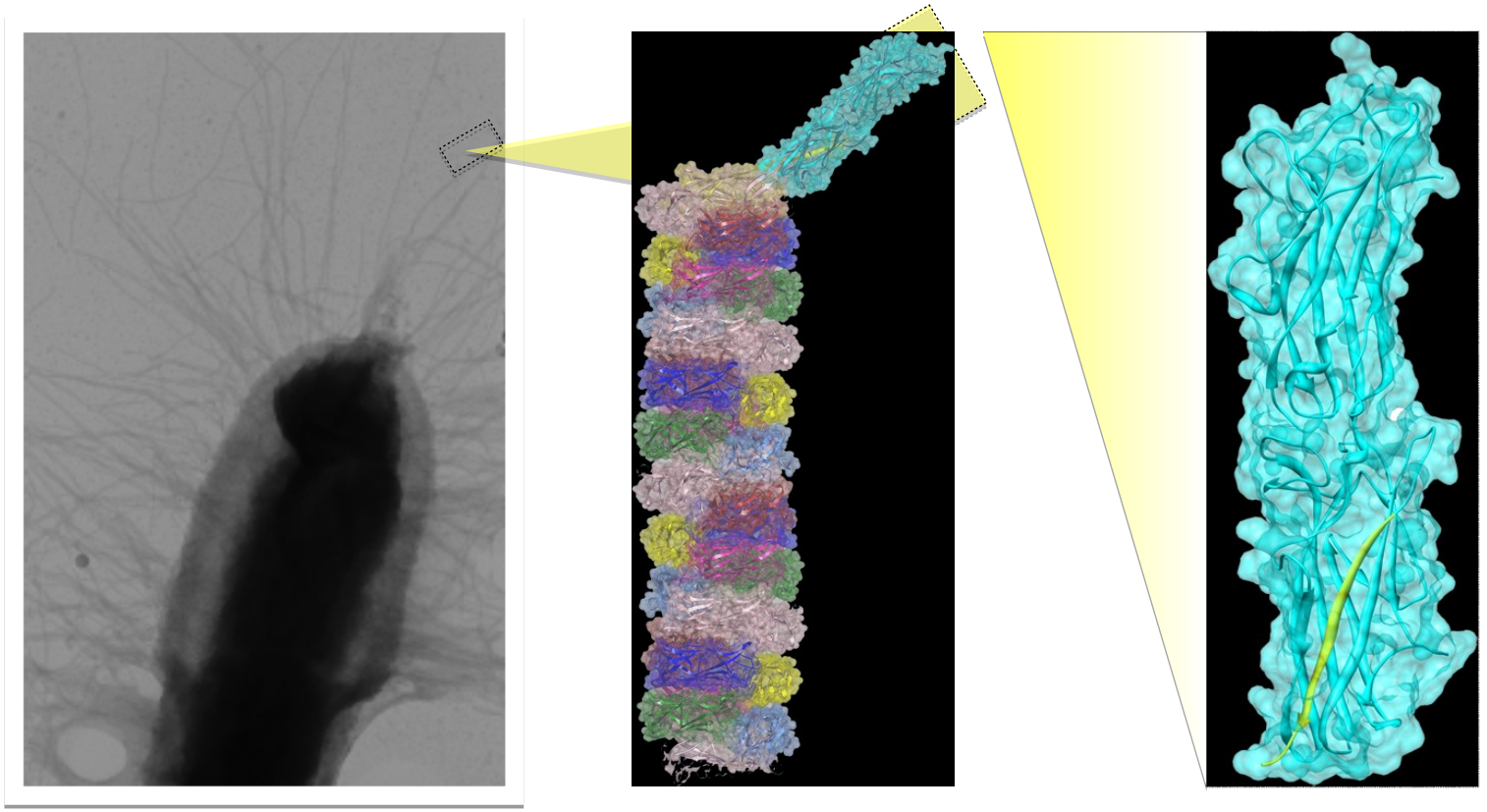
Clear, clinical proof has yet to accrue for any ETEC vaccine

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- Adhesin-based vaccine
  - Tip-localized adhesin ascribed role in intestinal binding
  - Adhesins exhibit greater antigenic conservation than major pilus-forming subunit
  - Recombinant adhesin variants developed, which are
    - Stabilized in native conformation
    - Highly immunogenic when given by mucosal and skin vaccination with adjuvant
    - Prototype adhesin (dscCfaE) proven as protective antigen

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- ETEC:



Whole-cell ETEC

CFA/I Fimbria

dscCfaE Adhesin

Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- NHP Model: Proof of efficacy for ETEC adhesin-based vaccine
  - Nonhuman primate ETEC diarrhea model established in *A. nancymaae* that mimics human disease
    - Challenge models established with CFA/- ETEC type strain
    - Intranasal vaccination with dscCfaE alone or with LTB (CTB) elicits significant protection
    - Result: 83% protective efficacy using dscCfaE with LTB

Vaccines Against Bacterial Diarrhea and Dysentery – ETEC

- Oral, passive protection with bovine milk IgG
  - Vaccinate pregnant cows with dscCfaE to g hyperimmune colostrum
  - Isolate hyperimmune bovine IgG (BIgG)
  - Two days before challenge take 3 oral doses/day BIgG at meals
  - Challenge with ETEC (homologous strain 1 x 10^9 cfu)
  - 10 human subjects, ----7 fully protected, 2 with mild diarrhea, 1 with moderate diarrhea, 0 with severe
  - 11 placebo subjects, ---- 9 with diarrhea, (6 severe, 1 moderate, 2 mild)

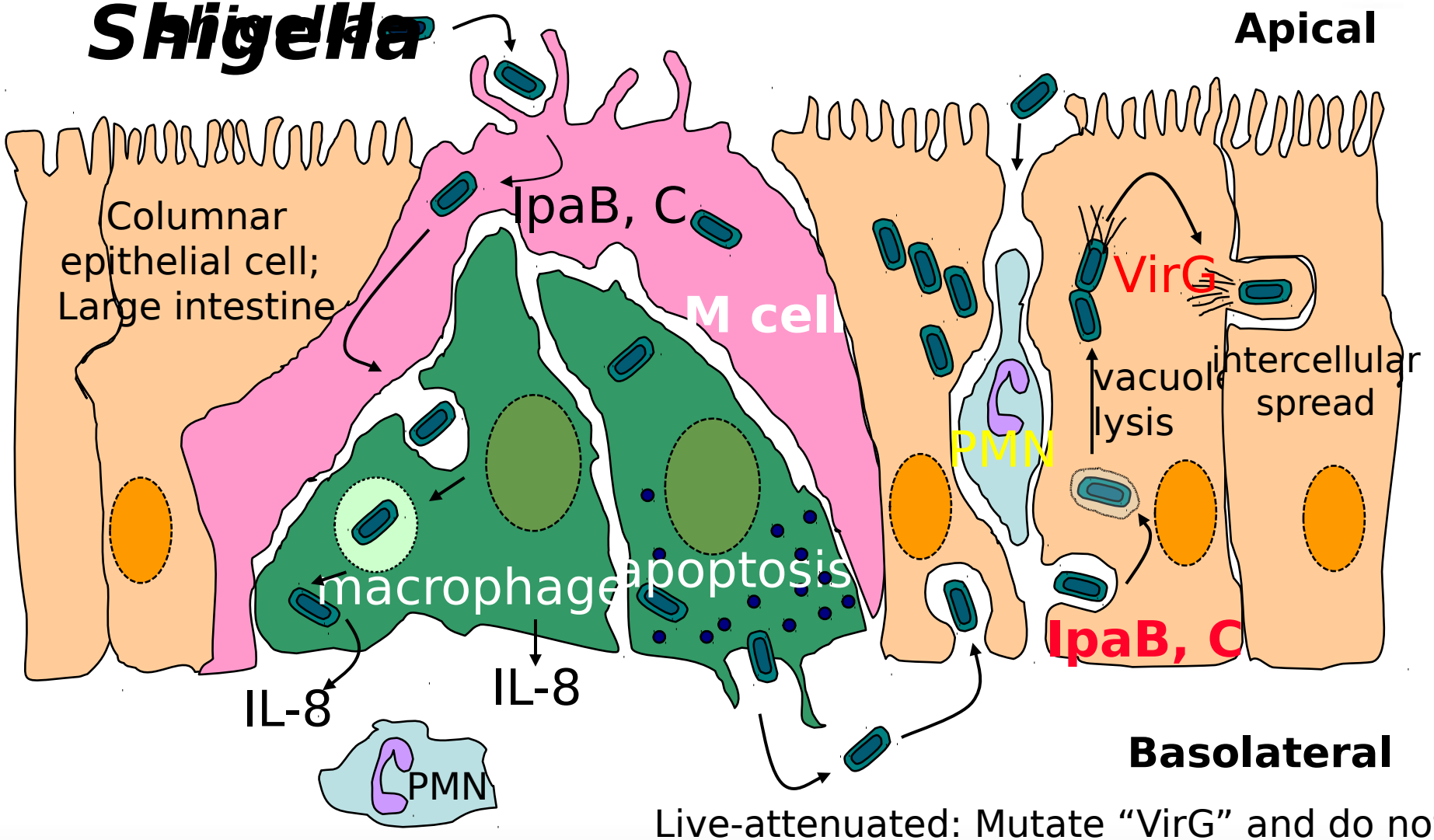
Vaccines Against Bacterial Diarrhea and Dysentery - ETEC

- A first-in-human Phase 1 clinical trial of the prototype ETEC adhesin (dscCfaE)
  - scheduled to begin in 2011,
    - active, skin patch vaccination
    - Challenge
- The adhesin-based vaccine IP has been licensed to sanofi pasteur (sp) vaccines
  - expanded preclinical evaluation of the components of a pentavalent adhesin-based ETEC vaccine
- US Army, NMRC, sanofi pasteur, PATH (nonprofit)

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

- Shigellosis / Dysentery
  - Person-to-person, foodborne (food, water)
  - Inoculum size --- 10-200 organisms
  - Serotype diversity --- >50 different serotypes (LPS)
  - Pathogenesis --- invasion, spread, inflammatory response with cytotoxicity
  - Clinical syndrome --- dysentery

Vaccines Against Bacterial Diarrhea and Dysentery – *Shigella*



Live-attenuated: Mutate “VirG” and do not get further spread of infection

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

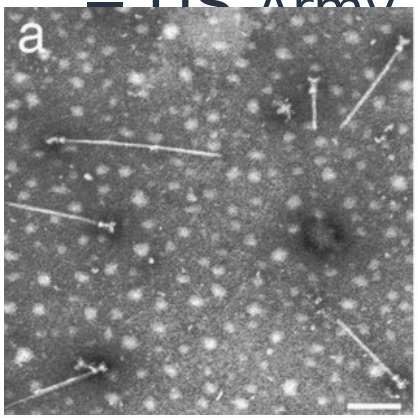
- *Shigella* vaccine strategies
  - Live, attenuated *Shigella* vaccines (LASV)
    - Virulence-based mutations (*vir*G) in *Shigella* (WRSS1) and further mutate toxins and immunomodulators (shET and msb) for less reactogenicity to create second generation vaccines (WRSs2 and WRSs3)
  - Recombinant
    - Invasion plasmid antigen (Ipa) proteins of Type Three Secretion System (TTSS) cloned, expressed and purified and added to *Shigella* LPS to create the “Invaplex” vaccine

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

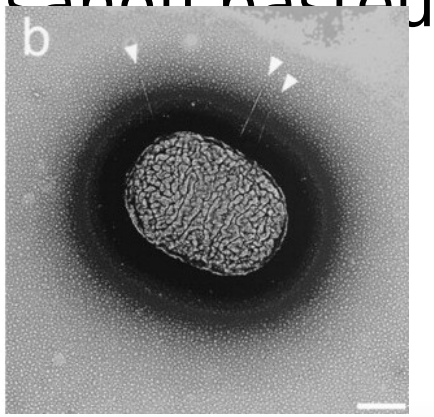
- Live attenuated *Shigella* vaccines
  - WRSS1 given to more than 100 volunteers, found to be safe and highly immunogenic but some side effects
  - WRSs2 and WRSs3 in phase 1 clinical trial to be conducted in April, FY11
  - To determine safety and immunogenicity
  - US Army, NIH funded

Vaccines Against Bacterial Diarrhea and Dysentery - *Shigella*

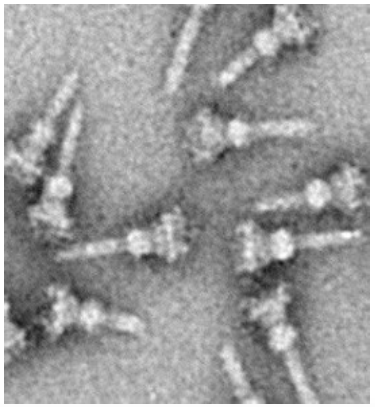
- Recombinant *Shigella* "Invaplex" vaccine
  - Cloned and purified proteins from the Type Three Secretion System (TTSS) mixed with *Shigella* LPS
  - Produces protective immune response in mice and guinea pig
  - Phase 1 clinical trial scheduled for F
  - US Army, sanofi pasteur



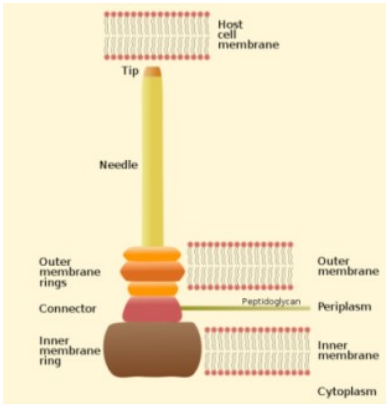
Injectisome



Injectisome extending



Injectisome



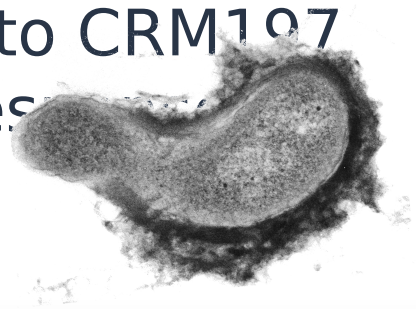
Injectisome graphic

Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

- *Campylobacter jejuni*
  - Transmission: Foodborne
  - Inoculum size: low ($\geq$ 5 x10^2 orgs)
  - Reservoirs animals (poultry)
  - Serotype diversity 48 Penner serotypes
  - Pathogenic process adherence, invasion, inflammatory response
  - clinical syndrome acute inflammatory response
  - sequelae reactive arthritis, Guillian-Barre, irritable bowl syndrome

Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

- *C. jejuni* polysaccharide capsules (CPS) first identified by genomics
- Major determinant of Penner serotype
- Proven *C. jejuni* virulence factor
- Polysaccharide antigens have required protein conjugation to be efficiently immunogenic as vaccines
  - Pneumococcus (Prevnar) *H. influenzae* B (HiB)
- Conjugate by reductive amination to CRM197 protein to elicit T-cell dependent res



Vaccines Against Bacterial Diarrhea and Dysentery - *Campylobacter*

- NHP model to prove efficacy for *C. jejuni* CPS-CRM197 conjugate vaccine
  - *C. jejuni* diarrhea model established in *Aotus nancymaae* that mimics human disease
  - SC vaccination with CPS81-76-CRM197 conjugate + alum
  - 100% protection from homologous (same serotype) challenge
- IND submission in FY11 for capsule-conjugate vaccine, phase 1 clinical trial beginning of FY13

Vaccines Against Bacterial Diarrhea and Dysentery

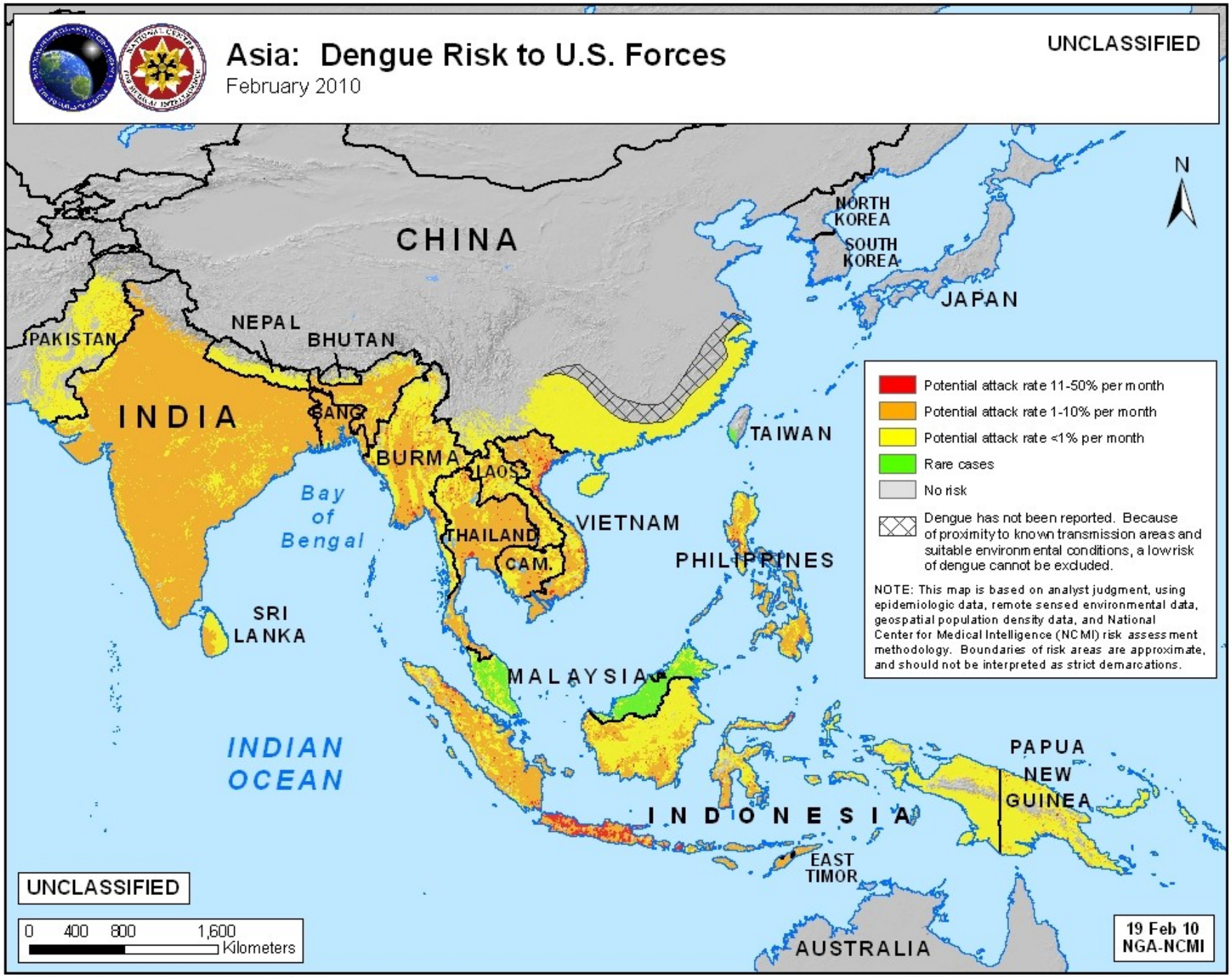
- Challenges
  - ETEC, *Shigella* and *Campylobacter* all have numerous serotypes
  - Each vaccine will have to be multivalent to cover relevant serotypes and to afford broad protection
  - The “Ideal” Diarrhea Vaccine will be multivalent, multi-pathogen

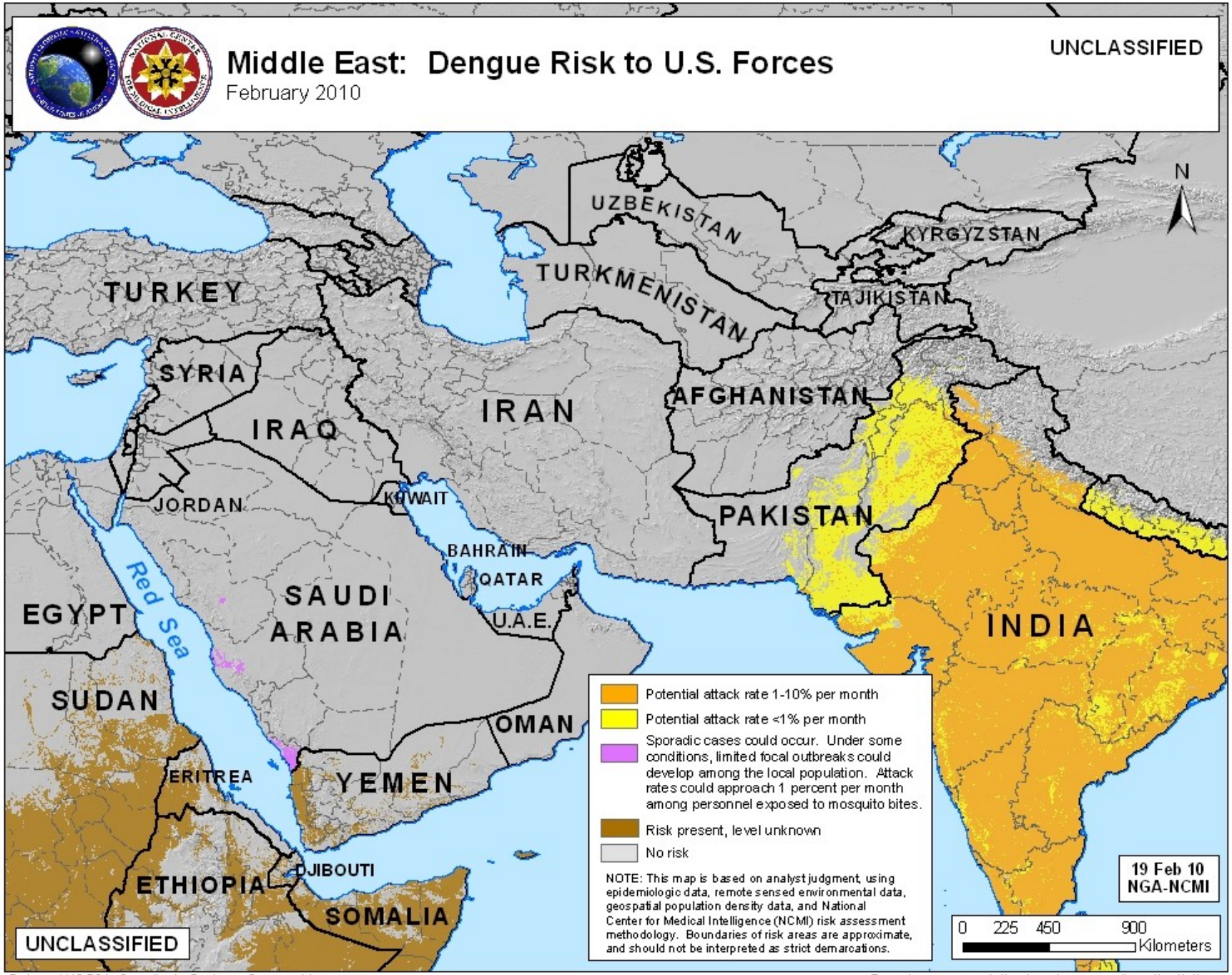
Summary

- Malaria
- Dengue
- Bacterial Diarrheal pathogens
- Challenges
  - Technical
  - Business
  - Cost
  - Time

Tetravalent Dengue Virus (TDV) Vaccine

Back-up Slides


Asia: Dengue Risk to U.S. Forces
February 2010
UNCLASSIFIED
N
CHINA
NORTH KOREA
SOUTH KOREA
JAPAN
PAKISTAN
NEPAL
BHUTAN
INDIA
BANG.
BURMA
LAOS
TAIWAN
Bay of Bengal
VIETNAM
THAILAND
CAM.
PHILIPPINES
SRI LANKA
MALAYSIA
INDIAN OCEAN
PAPUA NEW GUINEA
INDONESIA
EAST TIMOR
AUSTRALIA
Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
Potential attack rate <1% per month
Rare cases
No risk
Dengue has not been reported. Because of proximity to known transmission areas and suitable environmental conditions, a low risk of dengue cannot be excluded.
NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.
UNCLASSIFIED
0 400 800 1,600
Kilometers
19 Feb 10
NGA-NCMI
Datum: WGS84, Coordinate System: Geographic
Boundary representation is not necessarily authoritative.


Middle East: Dengue Risk to U.S. Forces
February 2010
UNCLASSIFIED
N
UZBEKISTAN
KYRGYZSTAN
TURKMENISTAN
TAJIKISTAN
TURKEY
SYRIA
IRAQ
IRAN
AFGHANISTAN
JORDAN
KUWAIT
BAHRAIN
QATAR
U.A.E.
PAKISTAN
INDIA
Red Sea
EGYPT
SAUDI ARABIA
SUDAN
OMAN
ERITREA
YEMEN
DJIBOUTI
ETHIOPIA
SOMALIA
Potential attack rate 1-10% per month
Potential attack rate <1% per month
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.
Risk present, level unknown
No risk
NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.
19 Feb 10
NGA-NCMI
0 225 450 900
Kilometers
UNCLASSIFIED
Datum: WGS84, Coordinate System: Geographic
Boundary representation is not necessarily authoritative.


South America: Dengue Risk to U.S. Forces
February 2010
UNCLASSIFIED
N
GUYANA
VENEZUELA
SURINAME
FRENCH GUIANA (France)
COLOMBIA
NORTH ATLANTIC OCEAN
ECUADOR
PACIFIC OCEAN
BRAZIL
PERU
BOLIVIA
CHILE
PARA.
SOUTH ATLANTIC OCEAN
ARGENTINA
URU.
Potential attack rate 11-50% per month
Potential attack rate 1-10% per month
Potential attack rate <1% per month
Rare cases
Sporadic cases could occur. Under some conditions, limited focal outbreaks could develop among the local population. Attack rates could approach 1 percent per month among personnel exposed to mosquito bites.
No risk
NOTE: This map is based on analyst judgment, using epidemiologic data, remote sensed environmental data, geospatial population density data, and National Center for Medical Intelligence (NCMI) risk assessment methodology. Boundaries of risk areas are approximate, and should not be interpreted as strict demarcations.
19 Feb 10
NGA-NCMI
0 275 550 1,100
Kilometers
UNCLASSIFIED
Datum: WGS84, Coordinate System: Geographic
Boundary representation is not necessarily authoritative.

Dengue Vaccinologist